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AUSTRALASIAN ANNALS OF MEDICINE

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CHRONIC NEPHRITIS IN QUEENSLAND[1]

D. A. HENDERSON

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DURING the past three years, an investigation of the incidence and ætiology of chronic nephritis in Queensland, with particular reference to its relation to plumbism in childhood, has been carried out. This paper will present the information derived from a study of mortality data. A follow-up investigation of cases of plumbism in childhood has already been published (Henderson, 1954), and a final paper dealing with clinical features and ætiology will appear at a later date.

HISTORICAL REVIEW

The first mention in the literature of a particular problem in relation to chronic nephritis in Queensland was in 1897. Halford, at a meeting of the British Medical Association, in the discussion which followed the delivery of papers on lead poisoning in children, observed that cases of granular contracted kidneys in young people aged under thirty years were more frequent in Brisbane than in the southern capital cities of Australia. Although practitioners were no doubt aware of the prevalence of the disease, nothing further was published until 1917, when Mathewson commented on a paper by Gibson on " plumbic ocular neuritis ". He stated that the mortality in Queensland from chronic nephritis was, in the fifteen to twenty years age group nine times, in the twenty to twenty-five years age group five to seven times, and in the twenty-five to thirty years age group nine times, that in Sydney, and related it to the high incidence of lead poisoning in Queensland children. There was no mention of the source of his figures.

In 1922, in an historical account of lead poisoning in Queensland children, the Council of the Queensland Branch of the British Medical Association made the following statement:

> There is a strong impression among some Brisbane practitioners that the prevalence of chronic nephritis among young adults in this city is partly a late result of the absorption of lead during childhood.

The first detailed comparison of Queensland mortality from the disease with that elsewhere was made in 1929 by Croll. His statistics were taken from the records of the Registrar-General for the ten-year period 1917 to 1926. They showed a much higher crude death rate in the under fifty years age group in Queensland than in New South Wales, Victoria and South Australia, which had similar rates. Croll estimated that during these ten years, 884 persons aged under forty years died in Queensland from chronic nephritis due to some factor not operating in the other States. His graph also shows that the crude death rate from chronic nephritis over the age of fifty years was less in Queensland than in the other States mentioned.

At the same time, Nye (1929) described the clinical features of the disease and presented evidence which led him to conclude that there was a close association between the chronic nephritis of Queensland and lead poisoning in childhood.

As a result of this article, the Queensland Branch of the British Medical Association wrote to the Commonwealth Department of Health urging the gravity of the problem and recommending the institution of a comprehensive inquiry. R. W. Cilento was appointed to conduct the inquiry. He was unable to complete it, and an Interim Report was presented in 1932 (Cilento, 1932). This contained a statistical section confirming the prevalence of chronic nephritis in this State.

[1] Received on December 22, 1954.

Cilento made use of the Registrar-General's mortality figures from 1907 to 1931, and showed that in Queensland throughout this period the death rate from chronic nephritis under the age of forty years was very high and increasing in magnitude. He noted that the rate over the age of fifty years was lower than in the other States of Australia, although the total death rate at all ages was the same in all States including Queensland. In explanation of this, he made the following suggestion:

> Whatever factor is producing the high death rate under 40 years of age from chronic nephritis in Queensland, since it does not increase the total mortality, appears merely to cull chronic nephritics at an earlier age.

Cilento also gave figures showing that although the excessive mortality under the age of forty years was highest in Brisbane and some other large cities, it was of wide distribution throughout the State. The investigation of ætiology was interrupted, and tentative conclusions only were reached. These were to the effect that lead poisoning in childhood, in conjunction with a number of other factors, appeared to be partly responsible for the chronic nephritis in young people in Queensland. The report stressed the possibility that undiagnosed scarlet fever might be an important ætiological agent.

In 1933, Nye criticized the Interim Report, minimizing the importance of scarlet fever, and gave additional evidence in support of his thesis that lead poisoning in childhood was the major cause.

At the request of the Queensland Government, the Walter and Eliza Hall Institute of Research in Pathology and Medicine assigned K. Fairley to review the whole of the evidence on chronic nephritis in Queensland. He (Fairley, 1934) concluded that lead poisoning in childhood accounted for part of the mortality from chronic nephritis in Queensland, but that further work was necessary to determine the magnitude of this part.

As a result, R. E. Murray resumed the inquiry by the Commonwealth Department of Health which Cilento had been unable to complete in 1932. The work was interrupted again, and a report of the investigation as far as it went appeared in 1939 (Murray, 1939). *Inter alia*, the following statements were made in the conclusions:

> Chronic nephritis is unduly prevalent among young people in Queensland. At the present time, about 90 people below the age of thirty years, and approximately the same number between the ages of thirty and fifty years, die annually in excess of the number that would succumb to the disease were the death rates the same as those of England and Wales.
>
> The evidence suggests that lead poisoning in childhood is a major factor in the causation of the abnormal Queensland incidence of chronic nephritis. Although it would appear that it is the sole factor responsible, it cannot be stated dogmatically that such is the case.

So the matter stood until the present investigation was begun in 1951.

NOMENCLATURE

The term "chronic nephritis" is used in a demographical sense in this paper and, except where otherwise stated, implies no single ætiological or pathological entity.

MORTALITY DATA

Mortality data for chronic nephritis in Queensland and the other States of Australia have been obtained from the Government Statistician for the period from 1875 to 1949. Death rates have been presented as average annual rates over ten-year periods. The ten-year periods have been selected to centre about the census years, and the census populations have been used in calculations. For the years from 1906 to 1949, rates for the other States combined were obtained by subtracting the Queensland deaths and populations from those in the whole of Australia compiled by the Commonwealth Bureau of Census and Statistics. Prior to 1906 when consolidated data for Australia were first published, the rates in New South Wales have been taken as equivalent to those of all other States. They are not available for 1889, 1891, 1892 and 1894. Rates for 1947 are an average of four years only.

Total Crude Death Rate from Chronic Nephritis

Figure I shows graphically the average annual total crude death rate per million persons over ten-year periods from 1875 to 1949. The rates for both Queensland and the other States of Australia show a gradual rise from about 110 in 1881 to about 500 in 1931. Subsequent to this year, they fell gradually to about 410 in 1947. As will be shown later, most of the deaths responsible for the increase have occurred in the upper age groups, and represent the general increase in degenerative disease of all kinds with aging of the population. The decline is general throughout the age groups and is largely due to the separation of "unspecified nephritis" as discussed below. Its acceleration in 1947 may be due to the four-year as opposed to the ten-year period, but in Queensland it is at least partly due to the decrease in deaths in the

younger age groups. Queensland's rate is lower than the other States to begin with, but exhibits a gradual relative increase, so that it is 53 less in 1891, 45 less in 1901, 18 less in 1911, five less in 1921, nine more in 1931, 22 more in 1941 and one more in 1947.

If, during the years from 1901 to 1947, the deaths in the under forty years age group in Queensland in excess of the rate in the other States are subtracted, the "corrected" rate remains steadily below that of the other States. This suggests that the crude rate in Queensland will be less than the rest of Australia when the present high incidence in the younger groups disappears.

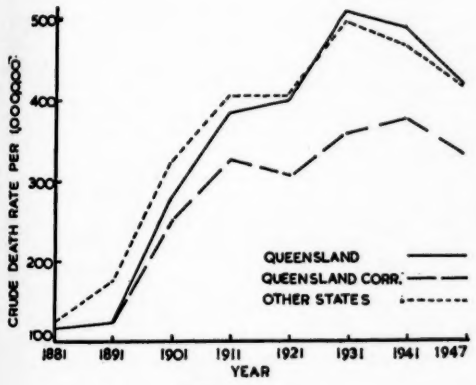

FIGURE I

Mortality from chronic nephritis. Average annual crude death rates of persons per 1,000,000 of population over ten-year periods from 1876 to 1949, in Queensland and the other States of Australia. Rates plotted as existing in the middle of the ten-year periods; 1947 rate is average of four years only. "Corrected" Queensland rates calculated after subtraction of the deaths which occurred below the age of forty years in excess of the rate in that age group in the other States. Arithmetic grid

Age-Specific Death Rates

Tables IA and IB and Figure II demonstrate the specific ten-year age group average annual death rates per hundred thousand for ten-year periods during the years from 1876 to 1949. The age groups have been separated in the figure for clarity.

Other States of Australia.—The general picture is the same for both sexes, and the rates increase successively with age. In the groups of age less than sixty years, there is an irregular rise to a peak at about 1901, followed by a gradual fall until 1947. The initial rise is difficult to explain at present, but probably depends on standards of diagnosis at the time and overlapping classification categories. Selection of population by the exclusion of sick persons in immigration may also have played a part. In the oldest groups, the rate rises until the period from 1931 to 1941. The deaths in these groups are largely responsible for the rise in total crude rate mentioned above. Previous selection of population by immigration, and more accurate diagnosis which transfers deaths from other categories such as senility, may play a part in this rise. Rates for males and females are much the same in each age group, except that they are higher for males in the two oldest groups.

Queensland.—The Queensland graphs are quite different. The male and female rates are similar, although the female rates are slightly higher in the younger age groups and the male in the older groups. The female graphs will be discussed as representative of both sexes. In the ten to nineteen years group, there is a gradual rise in the earlier years to reach a peak in 1931, when the rate was 16·9 compared with 3·1 in the other States. This rate of 16·9 represents approximately 12 deaths annually in excess of those which would occur in Queensland if its rate were the same as the other States. After 1931, the rate falls to 3·5 in 1947. The twenty to twenty-nine years group rate reaches a peak of 51·5 in 1931 compared with 7·6 in the other States—an annual excess in Queensland of approximately 32 deaths. In the thirty to thirty-nine years group, the 1931 rate was 52·3 in Queensland and 19·1 in the other States, giving an annual excess of about 21 deaths. The peak rate in the forty to forty-nine years group was 64·8, representing 13 extra deaths in Queensland above the rate in the other States of 39·1. In the fifty to fifty-nine years group, the 1931 rate was 79·5 in Queensland and 61·4 in the other States, giving about four extra deaths per year. Thus, during the period from 1926 to 1935, there was, among the female population of Queensland aged from ten to fifty-nine years, an annual excess of 82 deaths, or 27 per 100,000 population of this age, over those which would have occurred at the same rate as the other States. Similar but slightly lower figures apply to males.

In the two oldest age groups, the death rates follow the same general pattern as the other States, although they are consistently below them.

It will be noted that there has been a decline in mortality in Queensland in recent decades. The decline is better illustrated in the female graphs. It begins after 1931 in the ten to

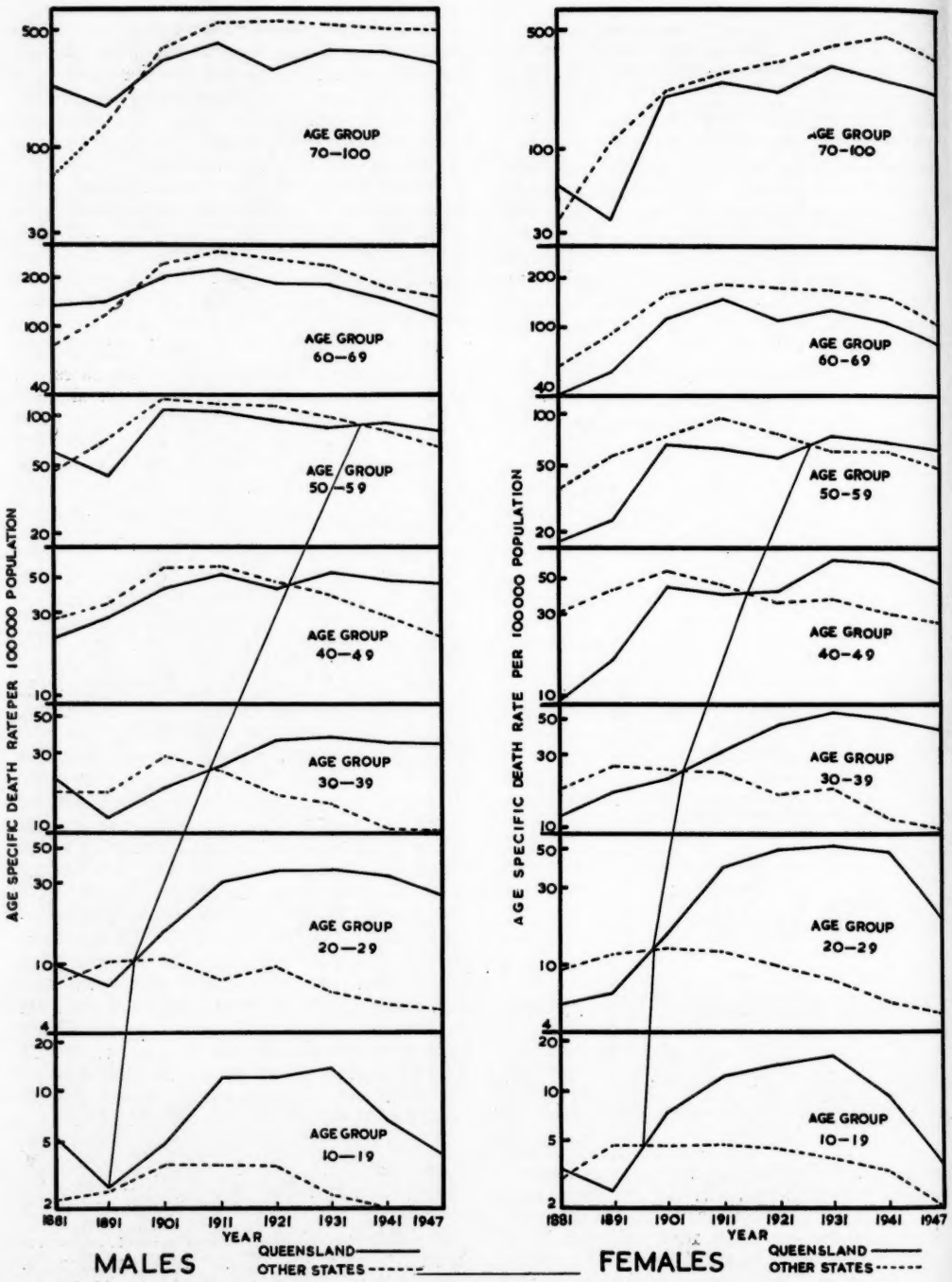

FIGURE II

Mortality from chronic nephritis. Average annual age and sex specific death rates per 100,000 of population in ten-year groups over ten-year periods from 1876 to 1919, in Queensland and the other States of Australia; 1947 rate is average of four years only. Semi-logarithmic grid

TABLE Ia

Chronic Nephritis Mortality : Average Annual Number of Deaths and Age-Specific Death Rates per 100,000 in Ten-Year Age Groups and Ten-Year Periods, of Males in Queensland and Other States of Australia

Age Groups (Years)	Deaths	1876 to 1885		1886 to 1895		1896 to 1905		1906 to 1915		1916 to 1925		1926 to 1935		1936 to 1945		1946 to 1949	
		Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States
0 to 9	Number	0·7	3·1	1·5	4·7	1·7	6·4	2·7	7·1	2·3	2·2	2·1	4·6	1·5	4·8	0·7	3·5
	Rate ..	2·3	3·1	2·8	3·1	2·7	3·9	3·9	1·6	2·5	0·4	2·3	0·8	1·5	0·8	0·6	0·5
10 to 19	Number	1·1	1·8	1·0	2·8	2·6	5·4	7·4	12·9	8·2	14·9	11·8	11·6	6·7	8·6	3·5	8·5
	Rate ..	5·2	2·1	2·6	2·5	4·8	3·6	11·5	3·4	11·5	3·4	13·1	2·2	7·5	1·7	4·0	1·7
20 to 29	Number	2·5	5·7	3·6	11·5	8·4	12·3	19·2	28·4	22·7	37·1	29·1	30·5	29·4	27·6	24·0	26·5
	Rate ..	10·0	7·6	7·3	10·2	17·0	10·8	30·6	7·7	34·1	9·8	35·0	6·5	33·4	5·5	26·8	5·1
30 to 39	Number	4·5	10·4	4·2	16·5	8·8	29·8	12·0	62·3	22·9	58·0	27·3	55·7	27·9	43·9	29·5	48·3
	Rate ..	21·0	18·5	11·5	18·1	19·5	29·8	26·2	22·4	37·0	16·0	37·4	14·0	34·4	9·6	34·5	9·7
40 to 49	Number	3·4	12·1	6·7	22·8	13·8	46·0	19·8	142·9	19·9	130·9	34·0	135·0	32·6	112·8	32·0	101·0
	Rate .	21·6	28·1	29·9	34·1	43·5	58·9	51·0	59·7	45·3	48·4	55·5	37·9	47·6	28·2	44·6	23·8
50 to 59	Number	3·8	10·8	6·1	28·2	20·5	57·9	26·7	193·9	33·5	253·2	36·7	244·2	45·2	246·6	46·0	214·5
	Rate ..	60·3	45·0	42·4	70·5	112·0	128·6	104·7	125·0	97·4	116·6	89·7	96·5	86·7	80·1	77·4	65·0
60 to 69	Number	3·2	9·8	7·8	23·9	22·6	70·5	30·7	219·0	36·2	218·9	50·3	625·9	50·5	364·8	49·0	379·2
	Rate ..	133·3	75·3	147·4	118·6	205·4	238·2	214·7	284·4	179·2	265·7	187·7	250·5	148·1	173·3	126·8	160·0
70 to 100	Number	1·6	4·4	3·3	14·5	13·0	54·7	30·7	286·0	26·6	325·9	59·5	559·9	77·2	731·4	74·2	697·2
	Rate ..	228·6	74·0	183·3	144·6	342·1	390·7	414·9	550·0	283·0	571·6	386·4	583·3	386·1	522·4	322·6	516·4

nineteen years ago group, then affects both the twenty to twenty-nine years group and, to a lesser extent, the thirty to thirty-nine years group after 1941. In the male graphs, the decline affected the ten to nineteen years group after 1931 and the twenty to twenty-nine years group after 1941, and has not yet reached the thirty to thirty-nine years group. The significance of this decline will be discussed later.

Summary.—Some factor has been operating in Queensland to cause the recorded death rate from chronic nephritis in the ten to fifty-nine years age group to be higher than that in the other States of Australia by a variable amount, which increased to a maximum of about 27 per 100,000 in the period from 1926 to 1935. In previous investigations attention was focused on the under forty years group, because the relative increase was greater and more obvious

TABLE Ib

Chronic Nephritis Mortality : Average Annual Number of Deaths and Age-Specific Death Rates per 100,000 in Ten-Year Age Groups and Ten-Year Periods, of Females in Queensland and Other States of Australia

Age Groups (Years)	Deaths	1876 to 1885		1886 to 1895		1896 to 1905		1906 to 1915		1916 to 1925		1926 to 1935		1936 to 1945		1946 to 1949	
		Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States	Qu'nsland	Other States
0 to 9	Number	0·7	2·7	1·6	2·8	1·2	5·5	1·1	7·0	1·2	2·7	1·7	4·0	0·8	4·3	1·0	2·7
	Rate ..	2·4	2·6	3·0	1·8	1·9	1·3	1·6	1·7	1·4	0·5	1·9	0·8	0·8	0·8	0·9	0·4
10 to 19	Number	0·7	2·0	0·9	4·2	3·9	5·6	7·6	14·4	10·4	15·5	14·6	15·5	7·8	12·6	3·0	9·0
	Rate ..	3·5	2·4	2·5	3·7	7·5	3·7	12·3	3·8	15·1	3·6	16·9	3·1	9·0	2·5	3·5	1·9
20 to 29	Number	0·9	5·8	2·4	11·0	6·4	15·0	21·0	41·9	32·2	39·7	38·3	34·8	36·0	27·9	15·0	24·0
	Rate ..	5·9	9·6	6·9	11·0	16·0	12·5	39·7	11·8	49·2	9·8	51·5	7·6	44·1	5·6	17·4	4·6
30 to 39	Number	1·3	7·9	3·5	16·2	6·6	21·7	11·4	62·0	24·8	57·9	33·7	76·4	34·6	57·0	34·2	52·7
	Rate ..	11·7	19·7	17·0	25·7	22·0	24·6	31·7	23·5	46·9	16·2	52·3	19·1	46·3	12·5	42·4	10·6
40 to 49	Number	0·7	8·3	2·2	16·2	9·0	31·8	11·2	94·4	15·5	94·5	33·9	133·7	37·9	120·1	31·7	107·0
	Rate ..	9·6	30·7	17·0	40·2	49·2	55·7	40·9	45·8	43·2	36·3	64·8	39·1	62·3	31·1	49·0	26·5
50 to 59	Number	0·6	4·9	1·8	14·8	7·7	26·4	10·7	120·3	13·3	152·6	26·8	150·5	35·6	188·5	37·2	164·7
	Rate ..	18·7	35·0	23·7	58·1	70·0	74·3	64·1	95·4	53·2	78·6	79·5	61·4	75·9	60·2	67·1	45·7
60 to 69	Number	0·5	4·5	1·7	10·8	7·2	33·3	12·0	135·1	16·5	202·3	29·8	294·2	35·8	279·9	29·0	257·3
	Rate ..	38·5	56·2	54·8	90·0	114·3	158·5	150·0	187·6	110·7	185·8	134·5	183·8	112·6	172·6	80·1	100·1
70 to 100	Number	0·3	1·9	0·4	7·3	5·4	23·7	12·4	141·1	18·3	203·8	37·0	412·8	47·2	623·9	50·0	600·0
	Rate ..	60·0	31·6	33·3	104·2	216·0	237·0	248·0	287·9	206·7	339·6	296·0	403·4	252·4	479·1	210·9	350·8

and did not occur in the fifty to fifty-nine years group until about 1935. The Queensland rates for ages over sixty years are consistently lower than those in other States.

Queensland Mortality Compared with that of the Other States of Australia

If the mortality in the other States of Australia is taken as the normal mortality from chronic nephritis, some very interesting deductions can be made from the graphs.

Let us consider when Queensland mortality first exceeded normal figures in the different age groups. This will be taken as the year in which the Queensland graphs cross those of the other States. Such crossing points, though not absolutely accurate, are adequate for purposes of comparison. In both males and females, the rates in the year 1881 will be ignored. All the crossings occur after 1891 in a period in which the mortality data were probably correct ; this will be discussed below.

In females, the Queensland line crosses normal in the ten to nineteen years age group in 1895, in the twenty to twenty-nine years groups in 1897, in the thirty to thirty-nine years group in 1903, in the forty to forty-nine years group in 1915 and in the fifty to fifty-nine years group in 1926, and does not cross normal or show any tendency to do so in the sixty to sixty-nine or seventy to one hundred years group.

In males, the crossing points occur in 1891, 1896, 1909, 1923 and 1936 in the successive age groups up to sixty years, and as in the females, the graphs show no tendency to cross in the ages over sixty years. The crossing points are connected by the thin line in the graphs.

Thus it may be said that the increased mortality in Queensland affected each age group at successively later dates, and examination of the intervals between these dates shows that within the limitations of statistics of this type, their average approximates to ten years.

This picture can be explained in only one way—that is, by an ætiological agent beginning to act on the children of Queensland in the period from about 1870 to 1880 and producing death from chronic nephritis in different persons in from ten to forty years. The children affected between 1880 and 1890 would begin dying when they were ten years older and forming part of the ten to nineteen years group, more of these would die ten years later when they are in the twenty to twenty-nine years group, and so on until the death of those occurring, say, forty-five years after the agent had acted upon them would raise the death rate in the fifty to five-nine years age group about 1930. The continued action of the ætiological agent would maintain the high rates in successive age groups as each ten-year " batch " or " cohort " of individuals became ten years older.

If the agent ceased to act, then the fall in mortality should commence in the youngest group and pass successively into the older groups, finally reaching the fifty to fifty-nine years group some fifty years later. It will be noted that the decline in mortality which has begun in Queensland is following such a pattern.

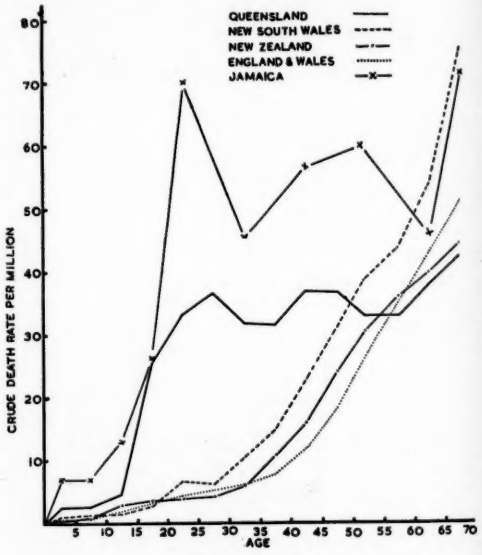

FIGURE III

Mortality from chronic nephritis. Crude death rates of persons in various countries by age groups, per 1,000,000 of total population. Averaged over period 1929 to 1934 except Jamaica (1931 to 1935). Data from Murray (1939). Arithmetic grid

The beginning of the decline in the ten to nineteen years group after 1931 indicates that the agent acted on many fewer children between 1920 and 1930 ; but the still high mortality in this group after 1941 shows that its disappearance was gradual, and even that it may still be present to a small extent. It may be anticipated that mortality will fall in each age group in turn, until that in the fifty to fifty-nine years group finally returns to normal in about 1990 to 2000. Then, provided that the agent has not reappeared in the meantime, all the individuals affected by it will have died and the problem of chronic nephritis in Queensland will cease to exist.

Geographical Distribution of Mortality from Chronic Nephritis.—Murray (1939) published graphs in his monograph comparing the Queensland mortality with that of New South Wales, New Zealand, England and Wales, and of Jamaica, for the years 1929 to 1934. His figures, which are average annual crude death rates by five-year age groups, have been replotted in Figure III. The comparability of statistical and diagnostic methods in the countries listed was not investigated. No explanation was offered for the high Jamaican mortality, and as population, standards of living and possibly age distribution of population are so different, careful verification and investigation would be necessary before one was made.

In view of the similarity in their populations, in the methods of training their medical practitioners and in their statistical classifications, it is probable that the mortality data in Australia, New Zealand and Great Britain at least, are comparable. Murray's figure, which illustrates the average annual specific five-year age group death rates in Queensland, New South Wales, England and Wales, although a more accurate representation of the mortality, merely confirms the picture presented by the crude rates. It will be noted that the curves of mortality in New South Wales, England, Wales and New Zealand are of the same type; but the Queensland curve shows a great excess of deaths in the younger age groups.

The geographical distribution of deaths from chronic nephritis within the State of Queensland was discussed by Cilento (1932) and by Nye (1933). Cilento gave data for the major cities and for country districts in the form of crude death rate by age groups for the years 1928 and 1929. Some of the numbers were too small to be statistically significant, but the general picture was that the high incidence under the age of forty years was widespread throughout the State; rates were higher in the cities than in the country districts, and Brisbane had the highest rate in the younger groups. Cilento drew some conclusions in relation to ætiology which appear unjustified, owing to the smallness of numbers and other factors to be discussed below.

Table II shows the average annual age-specific death rates in the four statistical divisions of Queensland during the years from 1945 to 1949. The high incidence in the younger groups is present in three of the districts, but absent in "inland, south of Tropic". In Murray's paper, crude age group death rates in the four districts for the period from 1933 to 1936 show the same relative incidence. The reason for the low rates in the south-western districts has not been investigated.

The geographical distribution of mortality means only that the individuals concerned died in particular areas. No accurate deduction of the geographical distribution within the

TABLE II

Chronic Nephritis Mortality: Average Annual Number of Deaths, and Age-Specific Death Rates per 100,000 in Ten-Year Age Groups in Statistical Divisions of Queensland from 1945 to 1949

Age Groups (Years)	Deaths	North of Tropic: Coastal	North of Tropic: Inland	South of Tropic: Coastal	South of Tropic: Inland	Metropolitan	South of Tropic: Coastal Less Metropolitan
0 to 9	Number ..	0·4	0·2	1·2	0	0·6	0·6
	Rate ..	0·8	0·3	0·9	0	0·8	0·9
10 to 19	Number ..	1·8	0	4·4	0·6	2·2	2·2
	Rate ..	4·7	0	4·3	2·4	4·0	4·6
20 to 29	Number ..	8·6	1·0	30·8	1·8	22·6	8·2
	Rate ..	23·2	19·6	27·5	7·5	33·2	18·6
30 to 39	Number ..	15·4	1·2	42·6	4·8	30·0	12·6
	Rate ..	45·0	28·5	39·8	20·8	47·6	28·6
40 to 49	Number ..	17·4	1·2	36·2	6·4	26·2	10·0
	Rate ..	50·8	34·3	41·1	35·5	50·4	27·8
50 to 59	Number ..	19·4	1·6	48·8	12·2	32·6	16·2
	Rate ..	84·3	59·2	64·2	87·1	69·4	55·9
60 to 69	Number ..	17·2	1·4	40·8	17·6	24·4	16·4
	Rate ..	122·9	87·5	78·0	176·0	76·2	78·1
70 to 100	Number ..	19·8	1·8	71·6	29·8	42·8	28·8
	Rate ..	241·4	191·1	216·9	426·0	214·0	221·5
Total population ..	.. ..	234,087	28,318	708,756	156,139	409,961	298,795

State of the ætiological agent can be made from mortality figures, as it acts many years before death, and considerable intra-State movement of population occurs. For example, of 179 persons below the age of forty-five years who died in the Brisbane General Hospital of chronic nephritis between the years 1945 and 1949, 70 were born outside of Brisbane. These 70 persons had made at least one move during their life-time, and it is possible that some of the remainder may have been absent from Brisbane when they were in contact with the agent, and returned to their native city to die.

A factor tending to promote the selective movement of chronic nephritics is the fact that the large cities, particularly Brisbane, are the medical centres of the State which have large public hospitals. Country people who died in the hospitals would be certified as having died in the particular city. However, a considerable proportion of people spend their lives in the area in which they were born, and it is probable that the ætiological agent was as widespread as the deaths indicate.

Although Queensland undoubtedly has many advantages to offer the other States, it has never been suggested that one of them is a more beneficial climate for chronic nephritics. Consequently there has been no reason for a selective movement of persons suffering from the disease to this State. Of the 70 persons mentioned above as having been born outside Brisbane, only five were born outside Queensland.

Summary.—There has been, in Queensland, a much higher incidence of deaths from chronic nephritis in persons aged under fifty years than in the other States of Australia, in New Zealand, in England and in Wales. Within Queensland this high incidence has been present in three of the four statistical divisions, the exception being " inland south of the Tropic ".

The Comparability of Mortality Data

There are a number of possible variables in the compilation of mortality data which may result in a lack of comparability between different statistical offices. The classification " chronic nephritis " in particular may be affected by these variables, as it comprises not one single disease entity, but a group of interrelated conditions. It is necessary to discuss in some detail the methods of compiling mortality statistics in Australia, to determine whether that in Queensland is truly comparable with that in the other States of Australia.

In broad outline, mortality statistics are prepared as follows: The medical practitioner attending the deceased person enters on the death certificate his diagnosis of the cause or causes of death. This certificate is forwarded to the government department registering deaths, whence the information it contains is sent to the statistical office. Here it is the responsibility of lay clerks to allot the death to one particular classification of cause and to present the deaths due to such classified causes in groups according to age, sex and other qualities required by the statistician. Two particular steps in this process may cause differences between Queensland and the other States of Australia and between different periods of time. These are the process of classification of deaths under a particular cause, and the diagnosis of the cause by the medical practitioner.

The former step involves, firstly, a classification of disease, secondly, a standard nosological index by which lay clerks can allot the varied nomenclature employed in certificates to the relevant classes and sub-classes of the classification, and thirdly, when a number of causes are entered on the certificate, some system of priority which enables a death to be classified under the principal cause.

Lancaster and Willcocks (1950) discussed in general the methods of classification employed in Australia, and confirmation, as far as Queensland is concerned, has been obtained from the Government Statistician in this State.

Up to 1906 the system of classifying causes of death in Queensland and New South Wales was identical with that used by the Registrar-General of England and Wales. As from January 1, 1906, all States of Australia, and the Commonwealth Bureau of Census and Statistics, agreed to use the Bertillion classification, which on further decennial revisions became the International List of Causes of death. Causes of death in Australia as a whole were first published by the Commonwealth Bureau of Census and Statistics in 1907 and were henceforth based on the International classification. The periods for which Australian mortality statistics were published on the basis of the different classifications are shown in Table III (adapted from Lancaster), which deals with the years under review. It also contains the causes taken to represent chronic nephritis in the preparation of tables in this paper.

The nosological indices used by Queensland were identical with those used by New South Wales during the period from 1875 to 1906, and with those used by the Commonwealth Bureau of Census and Statistics in compiling

mortality data for the whole of Australia from 1907 to the present day.

Queensland and New South Wales followed the English principle in the selection of a primary cause from multiple causes up to 1906. This involves the selection of the cause preferred by the certifier, rather than the use of a more arbitrary system of priority such as America introduced later. The position after 1906 has been stated by Lancaster and Willcocks (1950) as follows:

> It is not now clear what rules of selection were followed, although it was probably on the American basis. The only recorded decision which can now be traced is that at the 1925 Conference of Statisticians it was resolved "that it was desirable in Australia in the classification of joint causes of death to follow as closely as possible the rules laid down by the Index of Joint Causes of Death issued by the U.S. Bureau of the Census in 1914, or the later revision thereof".

TABLE III

Year	Classification	Period for which Australian Medical Statistics were Published on Each Basis	Causes Equivalent to Chronic Nephritis
1875	Registrar-General, England and Wales	1875 to 1885	Nephria
		1886 to 1902	Bright's disease and uræmia
		1903 to 1906	Chronic Bright's disease
	Bertillion classification: Revisions by International Commission:		
1900	First ..	1906 to 1909	Chronic Bright's disease
1909	Second ..	1910 to 1921	Chronic Bright's disease
1920	Third ..	1922 to 1930	Chronic nephritis
1929	Fourth ..	1931 to 1939	Chronic nephritis
1938	Fifth	1940 to 1949	Chronic nephritis
1948	Sixth ..	1950 to date	Chronic nephritis

Queensland has certainly used the American manual since 1925, and it is almost certain that this State used the same methods as the Commonwealth between 1906 and 1925, as the reports of the Queensland Statistician contain references to the desirability of standardization of statistical practice.

When mortality statistics for a condition such as chronic nephritis are compared over a number of years in order to determine trends, it becomes necessary to find out whether changes in classification have affected the numbers of deaths under that cause. As methods of compilation were the same in Queensland and New South Wales in the early years, and in Queensland and Australia in the later years, such changes would affect both, and may be of two types.

Firstly, there may be an alteration in the causes classified under "chronic nephritis". Such a change, made in the 1948 revision, was so radical that mortality from this cause after the adoption of the revision by Australia in 1950 is not comparable with that before. This is due to the transfer from chronic nephritis of a number of causes formerly placed in its "arteriosclerotic" subdivision. In general, these causes represented renal disease secondary to hypertension and arteriosclerosis. As a result, deaths from chronic nephritis under the new classification are about a third less than under the old.

Secondly, there may be an alteration in the list of causes given priority in certificates containing multiple causes.

Alteration in trend due to either or both of these factors would have the quality of occurring suddenly in the year of introduction of the new classification, and can be found by examining the changes in the classification manuals and checked by observing sudden alterations in the general mortality trend.

Of the second, third, fourth and fifth revisions of the International Classification and their nosological indices covering the period from 1910 to 1949, only the fourth contained a significant change which was carried into the fifth. This was the transfer of a number of causes from chronic nephritis to form "nephritis unspecified". These were vague diagnostic terms applied to some manifestations of renal disease and included "uræmia", "inflammation of the kidney", "parenchymatous nephritis" and such terms.

An average annual total of 50 deaths in Queensland and 300 deaths in the other States were classified as "nephritis unspecified" during the period from 1933 to 1937. These totals represent approximately 10% of the number of deaths classified as due to chronic nephritis in the years immediately before the adoption of the fourth revision in 1931. Their removal accounts for the drop in the crude death rate after 1931 mentioned earlier in the paper. Ten of these deaths in Queensland and 30 in the other States occurred in the age group under forty years.

During the period from 1945 to 1949, in the under forty years age group "nephritis unspecified" in Queensland accounted for 0·7 death per 100,000 of the population per year compared with 15·6 from chronic nephritis, and in the other States it accounted for 0·8 death per 100,000 of the population compared with 4·2 from chronic nephritis. Prior to 1909 there does not appear to have been a major

change in classification. "Nephria" and "chronic Bright's disease" were the major groups. "Uræmia" was separated during the period from 1886 to 1902, but has been included in the total "chronic nephritis" in this paper. The other major groups of renal causes during the early period were "acute nephritis" and "other diseases of the urinary system".

Changes in trend can be checked in Figure IV. This shows the annual age-specific mortality from chronic nephritis in persons aged under forty years from 1875 to 1949 for Queensland and the other States of Australia. Plotting of the annual rate on an arithmetical scale provides optimum conditions for observing changes in trend. The graph for the other States is chosen

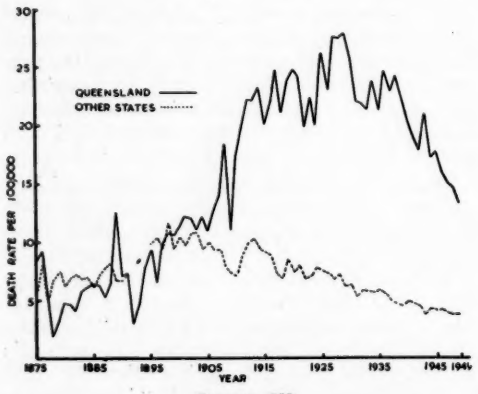

FIGURE IV

Mortality from chronic nephritis. Annual age specific death rates of persons aged under forty years per 100,000 population from 1875 to 1949 in Queensland and the other States of Australia. Arithmetic grid

to check on classification because a greater number of cases is involved, so that minor variations are smoothed out, and because there is no unusual problem in those States. It will be noted that since 1895 the general trend has been remarkably constant. A trough about 1910 is counterbalanced by a peak in 1913. There is no sharp change in trend in the years 1906, 1910, 1922, 1931 and 1940 when the different classification revisions were adopted.

Prior to 1895 there occurred a sudden change in trend in the form of an increase to almost twice the original rate. Its very suddenness, and the fact that it appears to affect the Queensland graph as well, suggest that this change is of statistical origin and not a reflection of the true mortality. It is very difficult to explain the change now, but it does not affect the arguments advanced earlier in this paper, as it occurred before the Queensland mortality began to rise.

With regard to the medical practitioners who made the diagnosis of causes of death, prior to 1940, when the first graduates passed through the University of Queensland Medical School, Queensland practitioners came from the southern and overseas medical schools in much the same proportion as those in the other States of Australia. Thus there was no difference between the two groups in undergraduate training, and their diagnostic abilities were probably equal. There was, however, a difference in the post-graduate experience of Queensland doctors which would have produced a difference in their certification of chronic nephritis as compared with that of their colleagues in the south.

This difference probably acted in two ways. Firstly, after Nye's paper was published in 1929, some Queensland practitioners would certify cases of chronic nephritis as "chronic plumbism" with no mention of renal disease, others as "saturnine nephritis" or "lead nephritis". Under the system of coding, lead poisoning has precedence over chronic nephritis, so that these deaths would not appear under "chronic nephritis", which would tend to reduce the true incidence of "chronic nephritis" in Queensland statistics. The magnitude of this reduction was not very great, as for the years from 1934 to 1937 an average of seven deaths yearly were classified as due to non-industrial lead poisoning.

Secondly, Queensland practitioners have had a much greater experience of chronic nephritis in young people. Being familiar with this rather clear-cut clinical picture in young people, they may tend to diagnose chronic nephritis less in older patients and essential hypertension and its sequelæ more often. In fact, the mortality from chronic nephritis in old people in this State is less than that in the other States, but so is the mortality from chronic nephritis *plus* vascular disease, as shown in Figure V; it is thus impossible to tell how important this factor has been. In any case, it would not affect comparability of mortality in the age groups below fifty years, when death from essential hypertension is relatively less common.

In general, the category "chronic nephritis" in the International classification is meant to represent a group of conditions whose common feature is non-suppurative inflammation and fibrosis of the kidney of long duration, with or without associated hypertensive cardio-vascular disease. In general, most of the diagnoses of causes of death are made on clinical grounds.

For example, in Queensland at present approximately 12% of all deaths are followed by autopsy, and in the years before the establishment of the Medical School the percentage was much less. In the other States with more medical schools it was probably higher.

The diagnostic clinical features of the "chronic nephritis" group are hypertension with its cardio-vascular complications *plus* albuminuria, to which may be added the

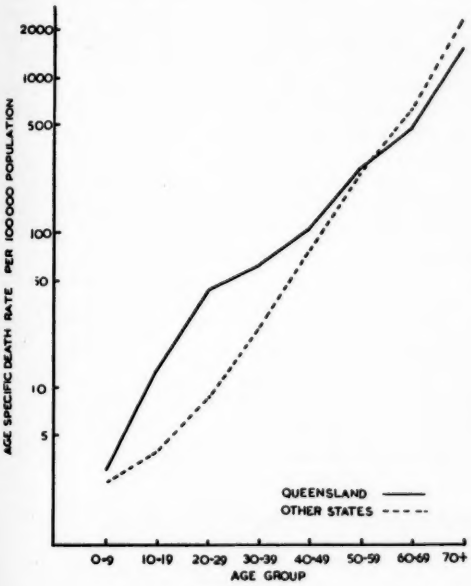

FIGURE V

Mortality from intracranial lesions of vascular origin, arteriosclerotic heart disease, hypertension, chronic nephritis and unspecified nephritis. Average annual age specific death rates of persons per 100,000 population in ten-year age groups over the period 1932 to 1949, in Queensland and the other States of Australia. Semi-logarithmic grid

manifestations of renal failure. A clinico-pathological analysis of such "clinical chronic Bright's disease" shows that it consists of three different groups of conditions: firstly, "chronic nephritis" or "nephrosclerosis", in which the renal lesion is primary and diffuse, hypertension and its effects being secondary; secondly, renal lesions resulting from hypertension and arterial disease; thirdly, a miscellany of diseases such as congenital renal abnormalities, amyloidosis, mechanical defects in the uro-genital tract, and other rarer conditions. The size of the third group is small in relation to the first and second. The first group contains most of the deaths under the age of forty years, and the majority of the deaths in the second group occur over the age of fifty years.

It will be shown in a later paper that the disease responsible for the high mortality from chronic nephritis in Queensland is one affecting primarily the kidney. It results in a grossly contracted kidney and manifests itself clinically as hypertension *plus* albuminuria, hypertensive cardiac disease, cardio-vascular accident, uræmia, either singly or more commonly in combination. In the majority of cases the clinical picture is clear-cut in the younger age groups and unlikely to be confused with other diseases. However, it is possible that Queensland practitioners have diagnosed these manifestations as chronic nephritis when they were due to another cause such as essential hypertension, or alternatively, that southern doctors have diagnosed primary renal disease as cardio-vascular accidents or hypertensive heart disease. The former would have the effect of increasing the deaths from chronic nephritis in Queensland at the expense of cardio-vascular accidents and hypertensive heart disease, and the latter would produce the reverse effect in other States. If there is no real difference in the incidence of any of these causes, then the total deaths due to them should be the same in both regions.

Figure V illustrates the average annual death rate over the period from 1932 to 1949, in ten-year age groups, for Queensland and the other States of Australia, from intracranial lesions of vascular origin, arteriosclerotic heart disease, hypertension, chronic nephritis and unspecified nephritis. Tables published by Nye (1933) show similar figures for the period from 1922 to 1932.

The mortality in Queensland up to the age of fifty years is greater by an amount approximately equal to the difference in the mortalities from chronic nephritis. Over fifty years, the Queensland mortality is less than that in the other States. Consequently, there is no fallacy due to misdiagnosis of vascular and renal disease allied to chronic nephritis.

The higher incidence of chronic nephritis in Queensland in the younger groups, combined with the lower incidence in the older groups, led Cilento (1932) to suggest that the ætiological agent did not add extra deaths in Queensland, but merely "culled" those susceptible to the disease at an earlier age. Reference to Figure II will prove that such an assumption was not justified, as the mortality in Queensland in the older groups has always been lower than in the other States, even before the population affected by the agent (that born after 1870) was old enough to have been "culled". The

shape of the curves at present suggests that the mortality in the older groups will remain relatively the same, and that there has been no "culling". The increased mortality in the fifty to fifty-nine years group supports this, but only the death rates over the next twenty years will prove it.

A more extensive check on the diagnosis of deaths under the age of forty years is provided in Table IV. Here the average annual death rates from all causes during the years from 1945 to 1949 inclusive are compared for Queensland and the other States of Australia. The under forty years group was chosen because the greatest difference in mortality from chronic nephritis occurs in it, and because the diagnosis of this condition cannot be confused with that of essential hypertension to a significant degree at this age. The only cause with a significantly different rate is chronic nephritis. In both males and females, the rate in Queensland is about four times that in the other States.

Reference has already been made to cardio-vascular conditions which may be confused with chronic nephritis. Gout, anæmia, œdema of the lungs, enteritis, toxæmia of pregnancy, unspecified nephritis and other diseases of the kidney (including chronic pyelonephritis) are other manifestations of chronic nephritis or other groups of diseases which may be involved in confusion of diagnosis. That this is not so is demonstrated by the similarity in death rates from Groups III, IV, VIII, IX, X (excluding chronic nephritis) and XI (see Table IV).

TABLE IV

All Causes of Death, Average Annual Number of Deaths and Age-Specific Death Rates per 100,000 of Males and Females Under the Age of Forty Years in Queensland and the Other States of Australia for the Period from 1945 to 1949

Group Number	Cause	Females				Males			
		Queensland		Other States of Australia		Queensland		Other States of Australia	
		Number of Deaths	Rate per 100,000	Number of Deaths	Rate per 100,000	Number of Deaths	Rate per 100,000	Number of Deaths	Rate per 100,000
I	Infections and parasitic diseases	81	22·5	600	30·0	95	25·4	563	28·0
II	Cancer and other tumours	43	11·9	258	12·9	35	9·3	202	10·0
III	Rheumatism, diseases of nutrition and endocrine glands, other general diseases and avitaminoses	23	6·3	116	5·8	22	5·8	96	4·8
IV	Diseases of the blood and blood-forming organs	12	3·4	66	3·3	14	3·7	87	4·3
V	Chronic poisoning and intoxication	2	0·6	2	0·1	4	0·9	9	0·4
VI	Diseases of the nervous system and sense organs	48	13·3	223	11·1	58	15·5	268	13·4
VII	Diseases of the circulatory system:								
	Arteriosclerosis	1	0·3	1	0·5	0·4	0·1	1	0·1
	High blood pressure (idiopathic)	2	0·5	16	0·8	2	0·6	7	0·3
	Other diseases of the circulatory system	30	8·2	168	8·4	41	10·8	246	12·0
VIII	Diseases of the respiratory system	75	20·9	423	21·1	88	23·5	484	24·2
IX	Diseases of the digestive system	64	17·7	278	13·9	80	21·4	342	17·1
X	Diseases of the genito-urinary system:								
	Acute nephritis	4	1·2	15	0·7	5	1·2	26	1·3
	Chronic nephritis	57	15·9	90	4·5	58	15·5	84	4·1
	Nephritis unspecified	2	0·6	6	0·3	3	0·8	5	0·2
	Other diseases of kidneys and ureters	4	1·1	14	0·7	2	0·6	15	0·7
	Other diseases of the genito-urinary system	5	1·3	19	0·9	2	0·6	6	0·3
XI	Diseases of pregnancy, childbirth and the puerperal states	46	12·8	222	11·1	—	—	—	—
XII	Diseases of the skin and cellular tissue	0·8	0·2	7	0·3	1	0·3	10	0·5
XIII	Diseases of the bones and organs of movement	1	0·2	2	0·1	1	0·2	8	0·4
XIV	Congenital malformations	57	16·0	313	15·6	67	17·9	380	19·0
XV	Diseases peculiar to the first year of life	203	56·6	1006	50·3	273	73·0	1385	69·0
XVI	Senility	—	—	—	—	—	—	—	—
XVII	Violent or accidental deaths	72	20·2	351	17·5	262	69·7	1339	66·2
XVIII	Ill-defined causes of death	6	1·6	13	0·6	5	1·3	18	0·9
	All causes	838	234·2	4209	210·4	1117	298·6	5581	279·0

If a large number of deaths occurred in the other States from causes as in Group I, which have precedence over chronic nephritis when they both appear in a certificate, the true incidence of chronic nephritis might be masked. The absence of such a high incidence of these causes, and the fact that chronic nephritics are no more liable to them in other States than in Queensland, preclude the possibility.

Table IV also shows the magnitude of the mortality from chronic nephritis in relation to other causes. Even during the period from 1945 to 1949 when the incidence was declining, it was one of the major causes of death in the whole under-forty years group, while in the thirty to thirty-nine years group the rate of 35 per 100,000 in males was second only to accidental death, and that of 42 per 100,000 in females was the highest of all causes. The death rate from chronic nephritis in the period about 1930 for the whole under-forty years group was even higher—approximately 24 per 100,000.

The annual age-specific death rates from chronic nephritis in the under forty years group in Queensland and the other States for the years from 1875 to 1949 are plotted in Figure IV.

Summary.—No statistical or diagnostic fallacy is responsible for the high incidence of deaths from chronic nephritis recorded in the mortality data of Queensland.

The Decline in Mortality from Chronic Nephritis in Queensland

Mention has already been made of a decline in the chronic nephritis mortality rate apparent in the younger age groups in Figure II. It is most important to find out whether this indicates a true decrease in the incidence of the disease, and to discover what course the mortality may be expected to follow in the future. If the decline is true and may be expected to continue until the mortality returns to normal, then the ætiological agent has ceased to act and public health authorities need only ensure that it does not reappear. If, on the other hand, the decline is not true and the high mortality in Queensland may be expected to continue, then the most strenuous efforts are called for on the part of these authorities to eliminate a disease which kills more people aged under fifty years than tuberculosis in all its forms. In either case it is necessary to determine the ætiology, and it must be shown that any agent suggested as being responsible conforms to the mortality trend in relation to its cessation or continuance.

The actual number of deaths is less in recent years, and the smaller rates are not due to population increase. The manner in which the decline has affected the ten to nineteen years group first and appears to be spreading successively to the older groups, is the pattern to be expected if an ætiological agent ceased to act on children aged under ten years. This is evidence in favour of the conclusion that the decline is true.

A possible explanation is to be found in the current fashion of diagnosing contracted kidneys as chronic pyelonephritis on histological criteria which are not specific. This would result in these deaths being classified under "other diseases of the kidney". Table IV shows that the mortality from "other diseases of the kidney" in Queensland was approximately one per 100,000 in the period from 1945 to 1949. Consequently there has been no increase in the number of deaths from this cause sufficient to account for the reduction of approximately eight per 100,000 in the mortality from chronic nephritis after 1940 shown in Figure IV. Thus the decline up to the present is true.

However, chronic nephritis is a disease of long duration between the original damage to the kidney and death. It may be that the decline was temporary, and that there are many young people alive with the disease in the community who are due to die in the next decade. The estimation of morbidity in a community is always a difficult problem, but the National Service registration and medical examinations provide a means of measuring it in one group of the community. This group comprises males aged eighteen years. All Australian youths are required by law to register when they reach this age. They are then medically examined and accepted or rejected for National Service. It is estimated that a very high proportion of youths do register. There is no reason why youths known to have chronic nephritis should try to avoid registration, as they have only to produce medical evidence of their disability to be rejected. A large proportion of those who would die of the disease in the next ten to fifteen years would have signs at the age of eighteen.

The records of the rejects from 18,000 examinations in Queensland and 43,000 in New South Wales performed during the same period have been searched. The examinations are made by boards of two practitioners in the various centres, and the percentage of rejections from all causes is remarkably constant in all States at about 5%. The results of the medical examination are recorded on a standard form, and there are four sections of the form which are relevant to this inquiry. These are as follows: (*a*) history of kidney trouble; (*b*) blood pressure

as recorded by the board; (*c*) presence of albuminuria; (*d*) comments of the board on reason for rejection. Relevant standards for rejection laid down are the following: (*a*) presence of chronic nephritis; (*b*) diastolic blood pressure over 90 millimetres of mercury; (*c*) albuminuria, at the discretion of the board; (*d*) history of acute nephritis within five years. There should be no significant variation between Queensland and New South Wales in the assessment of the signs. Practitioners generally are aware of the necessity of allowing patients to rest before accepting a high blood pressure. The urine is usually tested by the boiling test by orderlies in the large centres, but it is difficult to see why there should be any difference between the two States in the finding of significant amounts of albumin.

It is unlikely that chronic nephritics would escape rejection. In Queensland, at least, clinical experience is that a few patients, particularly in the early stages, may have intermittent albuminuria, and occasionally a patient with constant albuminuria may have a near-normal blood pressure. To allow for these, the causes of rejection have been grouped as in Table V. All the cases of chronic nephritis diagnosed as such, are included in the hypertension *plus* albuminuria group.

For each diagnostic group the figures for Queensland and New South Wales are similar, and it is concluded that the results of the National Service medical examinations indicate that, certainly in eighteen year old males, and probably in the rest of the young community, the incidence of chronic nephritis in Queensland has declined to the order of that existing in New South Wales.

All the senior physicians at the Brisbane General Hospital agree that their clinical impression is to the effect that chronic nephritis is becoming much less common in young people in Queensland.

SUMMARY

Since 1890, Queensland has had a higher mortality from chronic nephritis than the remainder of Australia. This higher mortality affected first the youngest age groups and then the older ones in succession, until the oldest to be affected—fifty to fifty-nine years—was involved in about 1930. The mortality has begun to decline in the youngest groups first, and if the present trend continues, as appears likely, the mortality in the fifty to fifty-nine years group should drop to that of the other States of Australia about 1990. All the statistical evidence adduced is in accord with clinical impression.

When the mortality was at its maximum, chronic nephritis was one of the most common causes of death under the age of forty years, and approximately 160 persons between the ages of ten and sixty years died each year in excess of the number who would have died, had the death rate from this disease been the same as that in the other States.

The excess mortality is best explained by the action of a nephrotoxic agent on the children of Queensland. Such an agent would have commenced acting about 1870 and gradually diminished after about 1920. It would initiate changes in the kidney which led to death from chronic nephritis in from ten to forty years in different individuals. Evidence will be published in a future paper indicating that this agent was excessive lead absorption in childhood.

ACKNOWLEDGEMENTS

Once again I wish to express my gratitude to my wife for her help in preparing the tables in this paper. Acknowledgements are also due to the staffs of the Queensland Government Statistician's Office and the Department of National Service in Brisbane and Sydney.

TABLE V

Number Rejected Because of Hypertension, Albuminuria, Hypertension plus Albuminuria, and History of Kidney Disease plus Hypertension, in Medical Examination of 43,000 National Service Registrants in New South Wales and 18,000 Registrants in Queensland

State		Hypertension	Albuminuria	Hypertension and Albuminuria	History of Kidney Disease and Hypertension	Total Rejections for These Causes	Percentage of Total Examinations
Queensland	Number of rejections	73	31	19	2	125	0·69
	Percentage ..	58·4	24·8	15·2	1·6	100	
New South Wales	Number of rejections	168	69	32	9	278	0·65
	Percentage ..	60·4	24·8	11·5	3·2	100	

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INDUSTRIAL LEAD POISONING IN RELATION TO CLIMATE.[1]

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APPARENTLY very little work has been done on the relationship of climate to the incidence of industrial lead poisoning.

The attention of the writer was drawn to this matter by the fact that the incidence of lead poisoning in relation to urinary lead concentrations appeared to be very different at Mount Isa, Queensland, where the climate is very hot and dry, from the incidence in Melbourne, where the climate is temperate.

At Mount Isa, out of 295 urinary lead determinations on persons engaged at Mount Isa Mines, Limited, in the mining, milling and smelting of lead ore, 13 yielded figures equal to or above 0·30 milligramme per litre. All the 13 persons who provided these samples were suffering from lead poisoning with disability as assessed by a medical board of three members. The diagnoses were based on the clinical condition, the stipple cell counts and other blood findings (anæmia *et cetera*), the concentration of lead in the urine, and the ratio of monocytes *plus* large lymphocytes to small lymphocytes. However, although the urinary lead concentration was used as an aid in diagnosis, it was not used as a definitive test.

Mathew (1929), referring to workers at Port Pirie in South Australia, stated that with the exception of one man, all who excreted more than 0·30 milligramme of lead per litre of urine showed definite evidence of lead poisoning. There were eight persons who excreted more than 0·30 milligramme per litre and one who excreted 0·30 milligramme per litre. Port Pirie has a much hotter climate than Melbourne.

In contrast with these observations at Mount Isa and Port Pirie, experience in Melbourne has been different.

I have reviewed the results of urinary lead determinations in Melbourne over a number of years. The specimens of urine were obtained from persons who were exposed to some industrial lead hazard (the great majority), or from persons who were suspected of having some significant exposure to lead, verification or otherwise of the fact being desired by the person referring the patient.

Of 936 determinations, 136 gave results equal to or greater than 0·30 milligramme per litre. These 136 specimens of urine were from 82 individuals. Of these 82 persons, 51 (or 62%) had evidence of lead poisoning at the time of the test, or within a short time (a few weeks) of it. The evidence included clinical signs and/or symptoms, or abnormal findings from other laboratory tests—for example, high stipple cell counts, anæmia, or a low ratio of large to small lymphoid cells.

Table I summarizes the information referred to above.

The numbers are not sufficiently large to justify firm conclusions; but the results at least suggest that the development of symptoms of lead poisoning in patients excreting significant amounts of lead in their urine is related in some way to climatic conditions. The symptoms are more likely to be present in hot climates. Other factors admittedly may influence the incidence of lead poisoning—for example, the period of employment—but data on this aspect are not available.

THE SEASONAL INCIDENCE OF INDUSTRIAL LEAD POISONING IN MELBOURNE

Since it appeared likely that there was some influence of temperature on the incidence of lead poisoning, it was decided to review the incidence of industrial lead poisoning in Melbourne, to see whether any confirmation could be obtained of the tentative ideas put forward above.

To this end 234 cases of industrial lead poisoning which occurred in Melbourne during the last sixteen years have been reviewed. This review has shown a very marked variation in incidence according to the season of the year (Table II).

Not all the subjects were completely incapacitated by acute symptoms; but all were in such a condition that removal from the lead hazard and treatment were advisable.

[1] Received on December 21, 1954.

TABLE I

The Relationship Between the Climate as Measured by the Maximum Annual Temperature and the Fraction of Those Subjects with Urinary Lead Content Equal to or Greater than 0·30 Milligramme per Litre Who were Suffering from Lead Poisoning

Place	Climate	Mean Annual Maximum Temperature (Degrees Fahrenheit)	Number of Persons with Urinary Lead Content of 0·30 Milligramme per Litre or Over	Number of These Persons Suffering from Lead Poisoning	Number Suffering from Lead Poisoning, as Fraction of Those with Urinary Lead Content of 0·30 Milligramme per Litre and Over
Mount Isa[1]	Hot nearly all the year	90·0	13	13	1·00
Port Pirie	Hot summer but mild winter	76·3	9	7	0·777
Melbourne	Temperate	67·6	82	51	0·622

[1] The temperature for Mount Isa is not available. The temperatures shown are for Cloncurry, which is close to Mount Isa, and has a very similar climate. The correlation coefficient between the mean annual temperature and the proportion of subjects with lead in their urine who were suffering from lead poisoning was 1. The figures for Mount Isa and Port Pirie are admittedly not large; but when allowance is made for this, there appears to be fairly close relationship between the climate and the incidence of lead poisoning among persons excreting 0·30 milligramme per litre and over in the urine.

In the great majority of these cases the diagnosis was confirmed by the Industrial Hygiene Division.

In Melbourne the hottest months are December, January and February, and the coldest June, July and August. It is clear that the incidence of lead poisoning is very much greater in the colder months than in the hotter.

TABLE II

The Numbers of Cases of Lead Poisoning Occurring in Each Month of the Year, and in Various Quarterly and Half-yearly Groupings, and the Mean Daily Maximum Temperatures for Each Month

Month	Number of Cases	Mean Daily Maximum Temperatures (Degrees Fahrenheit)	Quarterly and Half-Yearly Groupings	
January	11	79·25	January, February, March	44
February	13	77·7	April, May, June ..	77
March ..	20	75·1	July, August, September	66
April ..	20	67·3	October, November, December	47
May ..	25	61·9	December, January, February	34
June ..	32	56·36	March, April, May ..	65
July ..	24	56·1	June, July, August ..	79
August	23	58·4	September, October, November	55
September	19	63·64	March to August ..	144
October	20	67·43	September to February	90
November	16	71·12	April to September ..	145
December	11	81·2	October to March ..	89

The correlation coefficient between the mean maximum daily temperature for each month and the number of cases occurring in that month was $-0{\cdot}875$, which corresponds to a P value of less than 0·001. There was thus a very significant inverse correlation between the number of cases occurring each month and the mean daily maximum temperature in the month.

Many factors influence the occurrence of lead poisoning in industry. There are some which might be expected to vary, if only indirectly, with the temperature.

There are others for which this is not the case—for example, length of employment, individual idiosyncrasy, nature of the lead compound used. A person may commence work in a lead trade in any month. He may commence in January and by June have absorbed sufficient lead to be suffering from lead poisoning. On the other hand, he may commence in June and by December have become affected. Likewise, men may leave the lead trade in any month and seek employment elsewhere. It is considered that any effect on the incidence of lead poisoning which the latter factors may exert will be nullified because of the long period considered in this review, the very considerable number of persons working in the lead trades during this period, and the number of cases of lead poisoning which occurred amongst them.

Of the factors which might be expected to vary with the temperature, an obvious one is the concentration of lead in the air. In the colder months the doors and windows are more likely to be kept closed, so that general ventilation is decreased and higher concentrations of lead in the air are allowed to occur. However, other aspects of industrial hygiene are also operative.

The steps taken to improve conditions may result in considerable reduction in the concentrations of lead in air. On the contrary, slackening of care, breakdown of exhaust

equipment and so on may operate to cause increased concentrations of lead in air. It is obvious that these diverse factors may operate at any time of the year. To investigate this problem, 524 determinations of the concentration of lead in air in 39 different factories or works carried out during a period of about ten years were considered. Table III gives

TABLE III

Concentration of Lead in Air Throughout the Year

Month	Number of Determinations	Mean Concentrations of Lead in Air (Milligramme per Cubic Metre)
January	(9)	0·86
February	30	0·58
March	(9)	0·42
April	35	0·40
May	46	0·73
June	36	0·31
July	130	0·60
August	69	0·41
September	37	0·24
October	72	0·45
November	45	0·44
December	(6)	0·12
Total	524	—

these results of determination of the concentration of lead in air for each month of the year, and Table IV the results for half-yearly periods.

The correlation coefficient between the mean monthly concentrations of lead in air and the mean daily maximum temperatures for each month was 0·035, which was not significant.

TABLE IV

Distribution of Lead in Air Concentrations in Six-monthly Periods

Concentrations of Lead in Air (Milligramme per Cubic Metre)	April to September (353 Determinations)	October to March (171 Determinations)
Greater than 1·0 ..	6·7%	12·8%
Greater than 0·5 ..	26·6%	24·0%
Greater than 0·25 ..	50·58%	50·87%
Mean concentration	0·492 milligramme per cubic metre	0·476 milligramme per cubic metre

The number of determinations for January, March and December were too small for their means to be of much significance. If these are excluded, the correlation coefficient between the mean monthly concentration of lead in air and the corresponding mean daily maximum temperatures was 0·088, which is not significant.

In one factory engaged in lead refining from old battery plates, tests were carried out to determine the effect, if any, of open and of closed doors on the concentrations of lead in air. In this lead refinery the smelting furnace was situated at a distance from the north, south, east and west doors of the large shop about 36, 64, 20 and 30 feet respectively. A slight wind from the south was blowing on the occasion when the following observations were made.

At a position close to the east side of the smelting furnace, the concentration of lead in air with the north door open and the south, east and west doors shut was 1·2 milligrammes per cubic metre. At the same position with the north, south, east and west doors wide open, the concentration was 0·75 milligramme per cubic metre. However, at a position on the west side of this furnace, the concentration with the north door open and the other doors closed was 0·59 milligramme per cubic metre, and in the same position with all the doors wide open, it was 0·79 milligramme per cubic metre. At a position between the smelting furnace and the alloying pots the concentration with the north door open and the south, east and west doors shut was 0·15 milligramme per cubic metre, and with the north, south, east and west doors wide open it was 0·15 milligramme per cubic metre. Near the west alloying pot during drossing, the north door being open and the others closed, the concentration was 1·5 milligrammes per cubic metre. Near the east alloying pot during drossing, the north, south, east and west doors being open, the concentration was 1·2 milligrammes per cubic metre.

The number of the determinations is small; but from a knowledge of the kinds of processes producing the cases and of the circumstances and construction of the factories and plant, it is not considered that increased concentrations of lead in air are the sole cause of the increased incidence of poisoning in the cooler months.

The view that the increased incidence in Melbourne during the winter months is not due only to possibly increased concentrations of lead in air from lessened ventilation is supported of the facts recorded in the introduction to this paper.

Both at Mount Isa and at Port Pirie the works were very large and very largely open to the air, and not of the nature of the smaller type of workshop or factory in Melbourne. An indication of the size of these works is obtained from the facts that Mount Isa produced about 100 tons of pig lead per day, and Port Pirie

produced about 400 tons of pig lead per day from concentrates brought from Broken Hill.

In these places there would be no question of the concentration of lead in air varying according to the season of the year; and yet, as was indicated in the introduction, there is a very strong probability that the incidence of lead poisoning among persons excreting 0·30 milligramme per litre and over in the urine varied inversely with the temperatures in the three places.

Another obvious suggestion to account for the increased incidence in the cooler months is that increased production, which necessitates longer hours and/or the use of greater quantities of material, may occur in this period. This increased production occurs certainly in most of the accumulator factories; but in the other industries concerned the production rate is fairly steady throughout the year. It is not considered that this increased production in the winter months in the battery trade and the attendant increased exposure are the cause of the increased incidence in the winter months, since the ratio of the winter to summer cases in the battery industry is almost the same (actually slightly less) as in the other trades which have steady production throughout the year—namely, 1·60 and 1·676 respectively.

These facts are summarized in Table V.

TABLE V

Type of Trade	Nature of Seasonal Production	Cases in Colder Months	Cases in Hotter Months	Ratio of Number of Cases in Colder to Number in Hotter Months
All trades..	——	145	89	1·63
Battery ..	Considerably increased in colder months	88	55	1·60
Other than battery	Steady throughout year ..	57	34	1·676
Making lead arsenate	Steady throughout year ..	23	14	1·64

An explanation of the fewer cases in January may be that the Christmas holidays, during which men may be out of the hazard for periods from ten to twenty-one days, gives them a chance to recover somewhat from the effects of their exposure. However, this explanation fails in regard to the many fewer cases in November and December before the Christmas holiday spell.

There are two factors, either of which (or both) may operate to decrease the incidence of lead poisoning in the hotter months. One is the greater consumption of fresh fruit. Sodium citrate is known to increase the urinary excretion of lead, and possibly (though this is not proved), citric acid, malic acid and similar fruit acids may do so also.

Mount Isa is 600 miles west of Townsville in Queensland, and the surrounding country is dry and arid. Fresh vegetables and fruit are not in ample supply. Although the diet of those who took their meals in the company's messes was lavish, it is considered that that of

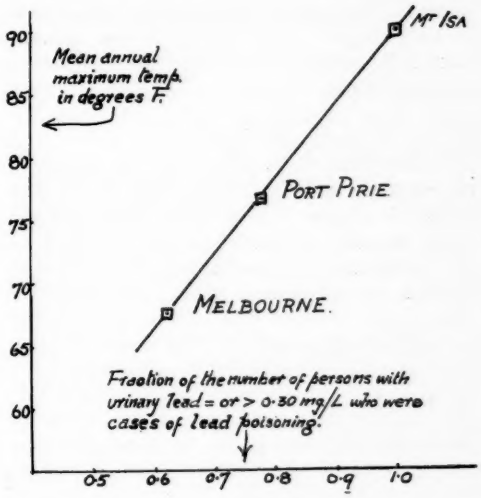

FIGURE I

many who lived in their own homes or in boarding houses was deficient in these things, and possibly also in fresh milk.

The other factor is the increased elimination of lead in the sweat during the hotter months.

Shiels (1954) has shown the importance of the sweat as a means for the elimination of lead. One may assume that at Mount Isa the daily excretion of fluid was of the order of one litre of urine and 2·5 to 3·0 litres of sweat per day. With 0·30 milligramme per litre of lead in the urine and a like concentration in the sweat, the total daily excretion in fluids would be greater than 1·0 milligramme of lead. In Melbourne the daily excretion of fluid may be assumed to be of the order of 1·5 litres of urine and 0·5 litre of sweat. With a concentration of 0·30 milligramme per litre of lead in the urine and a like concentration in the sweat, the total daily excretion in body fluids would be 0·60 milligramme of lead. In the former case the blood and organs and tissues of the

body would be in contact with more than one milligramme of lead per day, and in the latter with 0·60 milligramme of lead. There would thus be a greater chance of finding cases of lead poisoning among persons excreting 0·30 milligramme per litre of urine at Mount Isa than among those excreting 0·30 milligramme per litre in Melbourne.

On the other hand, from a constant amount of lead absorbed daily, more would be excreted in body fluids in the hotter months than in the colder, so that there would be less storage in the tissues. There would therefore be less chance of lead poisoning developing in the summer than in the winter if the conditions of exposure were the same.

SUMMARY

It has been shown that there is a greater incidence of industrial lead poisoning in Melbourne in the colder than in the hotter months.

Of persons excreting amounts of lead in their urine in a certain significantly high range, those in the hot climates of Mount Isa and Port Pirie show a greater incidence of lead poisoning than those in the cooler climate of Melbourne.

Various possible causes of this have been considered.

It is suggested that the increased elimination of lead in sweat may have an important bearing on these variations in the incidence of lead poisoning.

ACKNOWLEDGEMENTS

Acknowledgements are made to Dr. D. L. G. Thomas and Dr. K. H. Dudson for useful discussions, to the staff of the Industrial Hygiene Division for the lead in air determinations and laboratory tests relative to lead poisoning, to the Commonwealth Meteorological Bureau for supplying data of the temperatures, and to many medical practitioners who have referred cases. The number of these persons is too large to permit of individual mention.

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SEVERE ORTHOSTATIC HYPOTENSION[1]

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"Severe orthostatic hypotension" is an uncommon condition in which patients experience, when standing, a severe fall in blood pressure resulting in faintness, sometimes progressing to syncope. It is to be distinguished from numerous other causes of faintness in the erect posture, including the vasovagal attacks described by Lewis (1932) and the faintness on standing which may occur after prolonged recumbency and in various debilitating diseases. In orthostatic hypotension, the faintness on standing is persistent and the main disability, whereas in the other conditions it is usually temporary and disappears with improvement in the patient's general health.

The first report of a patient with symptoms from a marked fall in blood pressure when standing was presented by Laubry in 1924, and in the following year Bradbury and Eggleston (1925) described three further cases which were remarkably alike in that all patients had attacks of faintness or syncope when erect and there was little change in pulse rate accompanying the fall in blood pressure. Since these two publications there have been many reports of "postural" or "orthostatic" hypotension, all of which describe the same abnormality—a fall in blood pressure when the patient stands. However, analysis of these reports shows that many of the cases differ in certain important respects from those described by Bradbury and Eggleston.

The views of Nylin and Levander (1948) help to clarify the otherwise somewhat confused picture. These workers considered that orthostatic hypotension might result from two main faults—lack of venous tone with normal sympathetic reflexes ("sympathicotonic hypotension"), and loss of sympathetic reflexes ("asympathicotonic hypotension").

In the former type,[1] the fall in blood pressure is associated with tachycardia and vasoconstriction, sweating is maintained and the various vasomotor reflexes are present. In the latter, due to loss of sympathetic reflexes, pooling of even a normal amount of blood (as occurs in the erect posture) leads to hypotension. Tachycardia may or may not occur, according to whether the sympathetic nervous control of the heart is involved. In general, patients who have lost the normal ability to increase their heart rate are the more severely disabled, because they have lost another compensatory mechanism. Other sympathetic nervous functions may also be disturbed. According to Nylin and Levander, this "asympathicotonic" hypotension may be "primary"[2] (as in the cases described by Bradbury and Eggleston), may follow operations on the sympathetic nervous system, or may be due to endocrine disturbances such as Addison's disease. Orthostatic hypotension has been described not only in surgical interruption of sympathetic pathways (Jeffers, 1941; Johnson

[1] Received on July 7, 1955.

[1] We would include in this category the cases described by Bjure and Laurell (1927), Cases 3 and 4 of MacLean and Allen (1940), Case B.L. of Jeffers *et alii* (1941), the case of Corcoran *et alii* (1942), and the Cases 1, 2 and 4 of MacLean *et alii* (1944). In all these cases tachycardia accompanied the postural fall in blood pressure and there was no history of other sympathetic dysfunction.

[2] Among the "primary" cases we would include the three of Bradbury and Eggleston (1925), the two of Ghrist and Brown (1928), Case 2 of Laubry and Doumer (1932), Cases 1, 3, 4 and 6 of Chew *et alii* (1936), that of Korns and Randall (1937), that of Cappaccio and Donald (1938), that of Baker (1938), Case 1 of MacLean and Allen (1940), Case W.L. of Jeffers *et alii* (1941), the case of East and Brigden (1946), that of Nylin and Levander (1948), Case 2 of Verel (1951), the two cases of Rosecan *et alii* (1952), that of Crost and Friedlander (1952), and the two cases of Luft and von Euler (1953).

et alii, 1952), but also in various other neurological lesions—for example, *tabes dorsalis*, syringomyelia, hæmatomyelia, diabetic neuropathy (Ellis and Haynes, 1936; Springarn and Hitzig, 1942; Berner, 1952).

Various authors have discussed the nature and site of the lesion in orthostatic hypotension, with apparently conflicting opinions. A study of their papers shows that often they did not distinguish between the different types of this condition, and in fact sometimes included cases of the different types without differentiating between them. It is our object in this paper to describe four examples of the asympathicotonic group and the investigations we have performed to discover the nature and site of the lesion.

MATERIAL AND METHOD OF STUDY

During one year we examined four patients whose major complaint was faintness on standing, which was found to be associated with a considerable fall in blood pressure and little corresponding change in pulse rate. The patients were admitted to hospital, where, in addition to routine clinical examination and laboratory investigations, extensive tests were made of autonomic nervous functions.

To discover whether the lesion affected only the ability to maintain a normal blood pressure, a study was made not only of reflexes concerned in the regulation of blood pressure but also of other vasomotor responses and of other sympathetic and parasympathetic nerve functions. Sympathetic nervous functions are more accessible to investigation than parasympathetic functions, and these were accordingly studied more intensively, investigation of parasympathetic function being limited to pressure on the carotid sinuses and release of parasympathetic activity by injection of atropine.

The urinary excretion of noradrenaline[1] of two patients was assayed in order to assess overall sympathetic nervous activity. The response of the blood pressure to an intravenous infusion of noradrenaline was observed, to discover whether the blood vessels were capable of responding to the sympathetic transmitter substance. The vascular response to anæsthetization of peripheral nerves was studied, to learn whether sympathetic impulses were being transmitted along them.

Infusion of noradrenaline was omitted in Case II, because the patient became alarmed by the response from a small quantity injected intradermally in testing for sweating, and some tests were omitted in Case III.

Most tests were performed according to commonly accepted procedures and do not need detailed description. Pain was produced in Cases I, II and IV by the intramuscular injection of 15% sodium chloride solution. (In Case III this procedure did not produce pain, which, however, followed the squeezing of a hyperæsthetic area of the patient's abdominal wall.) Reflex hyperæmia, or vasodilatation from indirect heating, was estimated in the hand by measuring the heat elimination by calorimetry—as described by Barnett and Wigley (1953) and in the foot by measuring the blood flow by venous occlusion plethysmography—as described by Barnett (1950). Vasodilatation from anæsthetizing a peripheral nerve was indicated by a rise in the temperature, measured with a thermocouple. Sweating was tested by a starch-iodine method (Wada, 1950). Agents used locally in testing for sweating were acetylcholine, noradrenaline and pilocarpine, injected intradermally. The excretion of noradrenaline in the urine was measured by a biological assay, isolated rabbit intestine being used.

CASE REPORTS

CASE I.—A man, aged sixty years, had been well until about ten years previously, when he noticed that after moderate exertion, particularly in the morning and in summer, he developed blurred vision, weakness and lethargy, which were relieved by sitting for a few minutes. Also, he observed that he was sweating on the left side of his body only. Four to five years later his symptoms became increasingly severe: he suffered from several attacks of syncope when standing or after exertion, particularly in hot weather, and completely lost the ability to sweat. Although he had sometimes lost consciousness without warning, he had not hurt himself, but had twice been incontinent of urine. Neither the attacks of faintness nor those of actual syncope were associated with nausea or vomiting. They were relieved somewhat during treatment with DOCA and added salt, but in spite of this he was very uncomfortable in hot weather, when he was capable of very little exertion. He had been troubled by nocturia for several years, although, apart from the two episodes mentioned, he had retained control over bladder and bowel function. He had been impotent for the past three years.

The patient was a well-nourished, healthy-looking man. Apart from bilateral ptosis, clinical examination, X-ray examination of the chest and abdomen and electrocardiographic examination revealed no abnormality. The blood urea level was 40 milligrammes per 100 millilitres, and the serum electrolytes were normal. The eosinophile leucocyte count was depressed normally by an infusion of ACTH. On his changing from the lying to the sitting and standing posture there was a considerable fall in blood pressure, which was associated with little change in pulse rate (Figure I). This was not prevented by tight bandaging of the legs and abdomen, but was reduced considerably by arterial occlusion cuffs applied to the thighs.

[1] In this paper "noradrenaline" refers to the *laevo* form.

The intramuscular injection of ephedrine sulphate (30 milligrammes) produced only a slight rise of the patient's blood pressure and pulse rate. He was treated for successive periods of a few days by means of a "head-up" bed at night, extra salt (10 grammes of sodium chloride daily), the "head-up" position *plus* extra salt, the "head-up" position *plus* DOCA (five

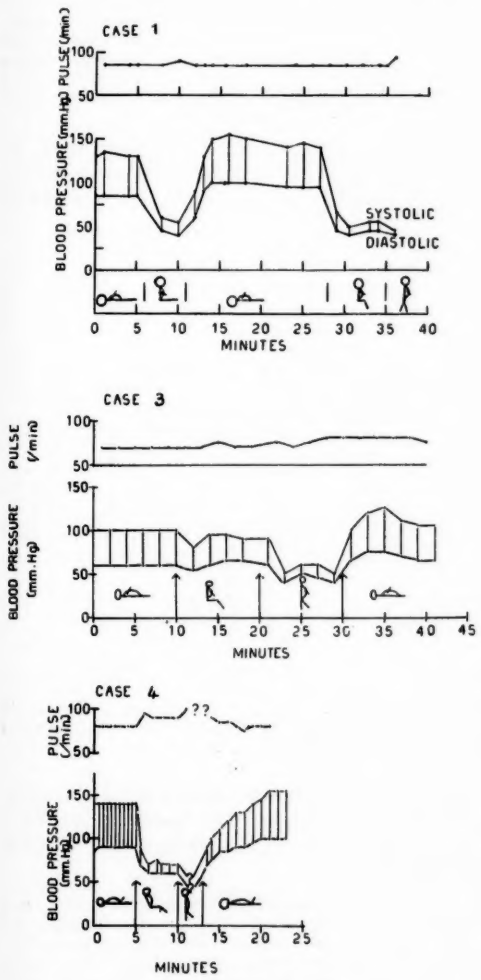

FIGURE I

Response of the blood pressure and pulse rate to change of posture

milligrammes daily), and the "head-up" position *plus* extra salt (five grammes daily) *plus* DOCA (five milligrammes daily). No significant improvement was noted until the end of the treatment period, when the patient could stand comfortably for nine minutes, whereas previously he had fainted within one minute; it seemed that the addition of DOCA gave most benefit. There was no relief of the orthostatic hypotension from an air-filled pressure suit and only slight benefit from a water-filled suit reaching to about the umbilicus. However, considerable relief resulted from immersion in a swimming bath to heart level (Figure II). On his discharge from hospital, the patient volunteered to try the effect of extra salt, of DOCA, and of DOCA *plus* the "head-up" position for three successive periods of four weeks, but none produced worthwhile benefit.

The results of important tests of the autonomic nervous system are summarized qualitatively in Table I, and certain responses are shown graphically and compared with those obtained in Cases III and IV in Figures III to VII.[1]

It is to be noted there was failure to maintain a normal blood pressure, not only in response to change in posture, but also during venous trapping, reactive hyperæmia, exercise and forced expiration (Flack, 1921). Cold and pain, which normally cause a rise in blood pressure, produced a fall. However, there was a considerable rise from an infusion of noradrenaline.[2] Vasomotor responses to temperature were absent (reflex hyperæmia test), and anæsthetization of an ulnar nerve was not followed by vasodilatation in the hand. The heart rate remained remarkably steady in spite of considerable falls in blood pressure and during exercise. However, it rose during an infusion of noradrenaline. Other sympathetic nervous responses such as sweating and pilo-erection were also lost (although pilo-erection followed the local injection of noradrenaline). The excretion of noradrenaline in the urine was very low (less than five microgrammes per litre). The injection of atropine (to remove parasympathetic activity) failed to produce tachycardia, although some dryness of the mouth and dilatation of pupils occurred. Pressure over the carotid sinuses did not cause a fall in pulse rate, although it resulted in a fall in blood pressure.

To sum up, the tests indicated a widespread loss of sympathetic nervous function, and no evidence was obtained of sympathetic impulses traversing a peripheral nerve. However, blood vessels, heart and smooth muscle were fully capable of responding to the sympathetic transmitter substance, noradrenaline. There was some evidence of loss of parasympathetic nervous function.

CASE II.—A single woman, aged sixty-one years, stated that for the past sixteen years she had been subject to attacks of fainting when standing, at first only when she got out of bed in the morning, but more recently at other times of the day as well. They were most frequent in the summer and during periods of emotional stress. Fainting was preceded by giddiness and blurring of vision and sometimes by jerking movements of her wrists and ankles; only once had an attack been associated with vomiting, and never with nausea. She had been incontinent of urine twice during these episodes, but on both occasions

[1] Many clinical data have been omitted for considerations of space. They will be supplied by the authors on request.

[2] Barnett and Fowler (1952), studying normal subjects, found that a rise in blood pressure of the extent noted in this patient required approximately twice the dose of noradrenaline.

she was on the way to the toilet. During the past sixteen years she had been readily fatigued and short of breath on slight exertion. Her appetite was poor in hot weather. She was habitually constipated. For the past year she had had to rise once at night to pass urine, but had no undue frequency of micturition during the day. She was troubled with chronic "nasal congestion". She did not ever remember sweating.

The patient was a somewhat pale, grey-haired, elderly woman with a dry skin. Her heart, lungs and abdomen were normal. Her blood pressure varied between 130 and 200 millimetres of mercury, systolic, and between 80 and 110 millimetres, diastolic, when she was recumbent; when she stood, it fell considerably within a few minutes, often to unrecordable levels. The pulse rate varied between 70 and 80 per minute and did not rise during the postural fall in blood pressure. She had a horizontal nystagmus when looking to the left, but no other neurological abnormality. X-ray examination of her chest revealed no abnormality. Electrocardiographic examination showed a left heart strain pattern. The hæmoglobin level was 11 grammes *per centum*, the leucocyte count was 7000 per cubic millimetre and the blood film was normal. The urine contained no albumin. The blood urea level was 80 milligrammes per 100 millilitres; the maximum concentration of urea in the urine after the administration of 15 grammes of urea was 1·5 grammes *per centum* (in a specimen of 85 millilitres); the urea clearance (Fowweather) was 30% of average normal. Of a water load of 1500 millilitres, 67% was excreted in five hours.

The patient was treated by means of a "head-up" bed without any significant effect. Ephedrine, given orally, one grain every four hours, had an inconstant effect on the postural hypotension and was not of great help. She has been relieved to some extent by wearing tight elastic stockings extending from her toes to her groins. Only slight relief of the postural hypotension was obtained with an air-filled pressure suit and by pressurized boots reaching to the thighs. As in Case I, great relief was afforded by immersion in water to heart level.

In general, the responses to the various tests of the autonomic nervous system were similar to those in Case I. Mention will be made only of the differences from this case. There was no fall in blood pressure from the cold pressor test, and the fall from pain and carotid sinus pressure was only slight. Although there was no sweating from body heating, it occurred to a varying degree from local injection of sweating agents. Moderate pilo-erection resulted from both cold and the local injection of noradrenaline. Peripheral nerves were anæsthetized in all four limbs (Figure VIII); in three there was no change and in the fourth a rise in temperature.

It is apparent that this case is very similar to Case I. The slight differences in responses were probably due to the fact that the loss of sympathetic nervous function was not universal, vasomotor responses being spared in one limb and other responses spared to a slight degree elsewhere.

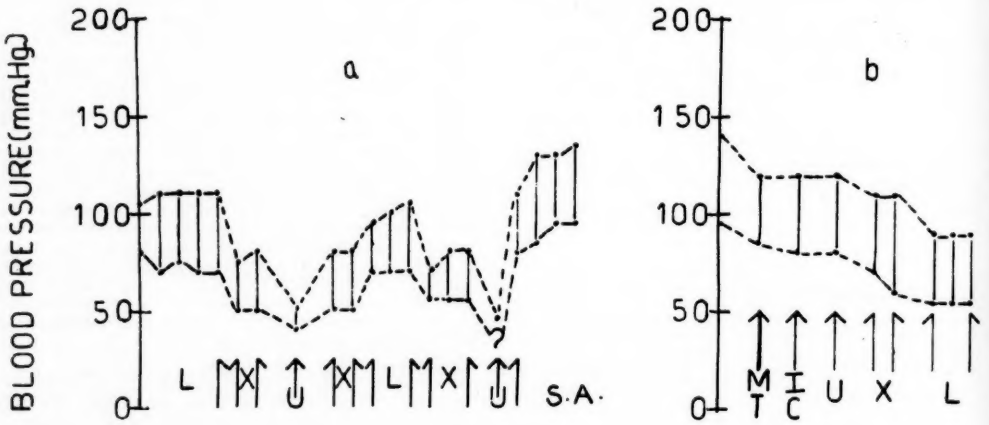

FIGURE II

(*a*) Effect of immersion in water on the orthostatic hypotension in Case I. L, water to angle of Louis; X, to xiphisternum; U, to umbilicus; S.A., to apex of axillæ with patient sitting. (*b*) Effect of immersion in water on the blood pressure of a normal subject (A.J.B.). M.T., water to mid-thigh; I.C., to iliac crest

CASE III.—A man, aged sixty-seven years, first experienced attacks of dizziness precipitated by standing two years ago; at first they occurred once every two to three weeks, but latterly two or three times a day. They began with "flashing lights before both eyes" and consisted of vertigo, "light-headedness" and, when severe and prolonged, loss of consciousness. He had never sustained injury, been incontinent of urine or bitten his tongue. During the same period he had noticed increasing weakness and tremor of his hands, shooting pains in both legs, dyspnœa on exertion, and, more recently, swelling of his legs. Although micturition was frequent he had good bladder control. He had been troubled by frequent attacks of diarrhœa for twelve months, and his bowels were apt to open involuntarily during micturition. He never developed palpitation on

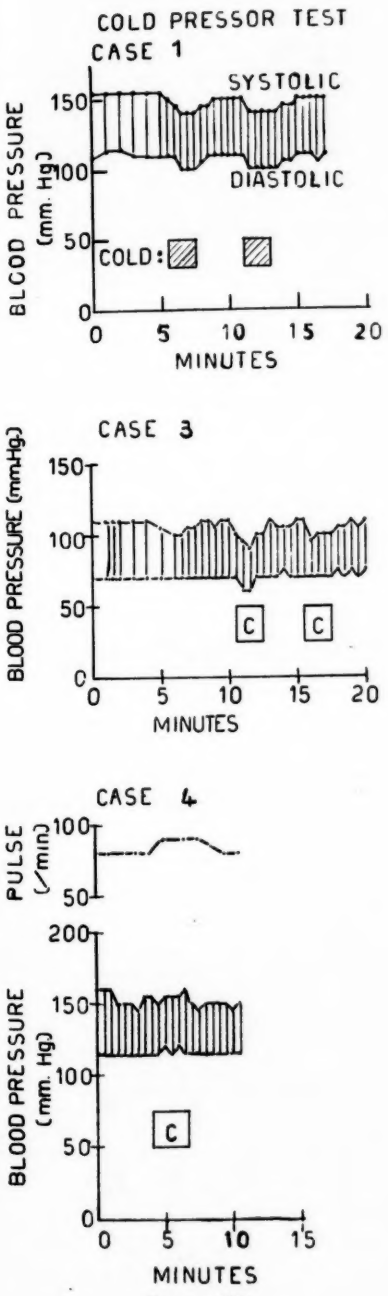

FIGURE III

Response of blood pressure and pulse rate to immersion of one hand in water at 4° C. for two minutes

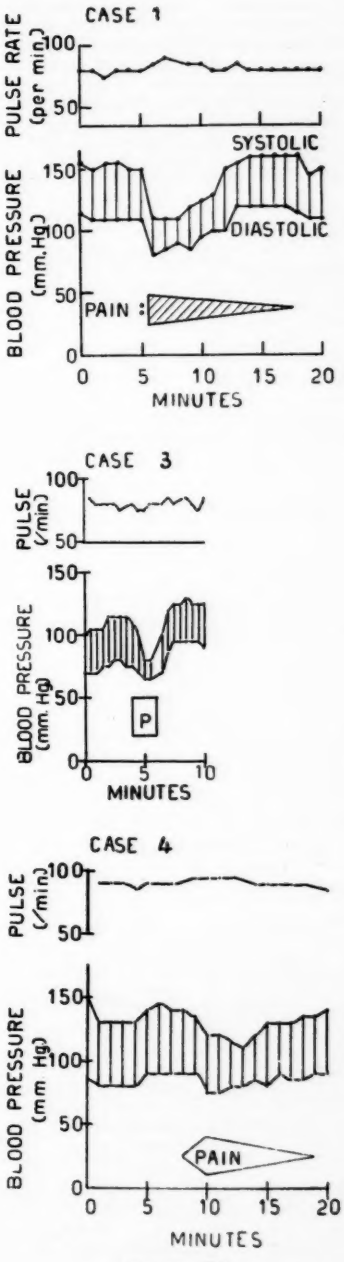

FIGURE IV

Response of blood pressure and pulse rate to pain, produced by intramuscular injection of hypertonic saline solution in Cases I and IV, and in pinching the abdominal wall in Case III

exertion or emotion. He sweated heavily in hot weather, particularly from the back of his left wrist, although never from his forehead.

The patient was a frail old man with œdema of the legs and slightly pale mucosæ. There was a considerable fall in blood pressure on standing, with little change in pulse rate (Figure I). His heart, lungs and abdomen were clinically normal. He had a normochromic anæmia, and occult blood was present in his stools. (No cause for this was found.) His

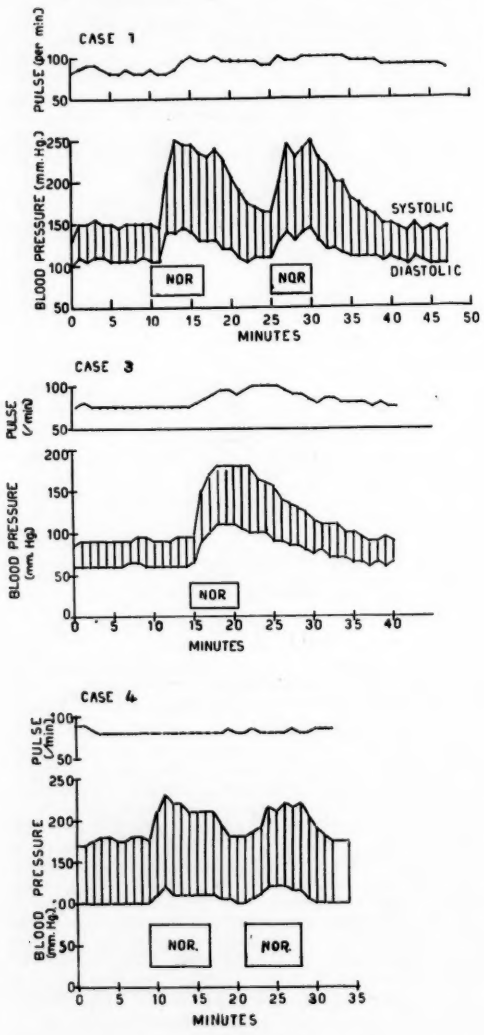

FIGURE V

Response of blood pressure and pulse rate to an intravenous infusion of l-noradrenaline (0·100 microgramme per kilogram per minute in Case I, 0·085 microgramme per kilogram per minute in Case III, and 0·110 microgramme per kilogram per minute in Case IV)

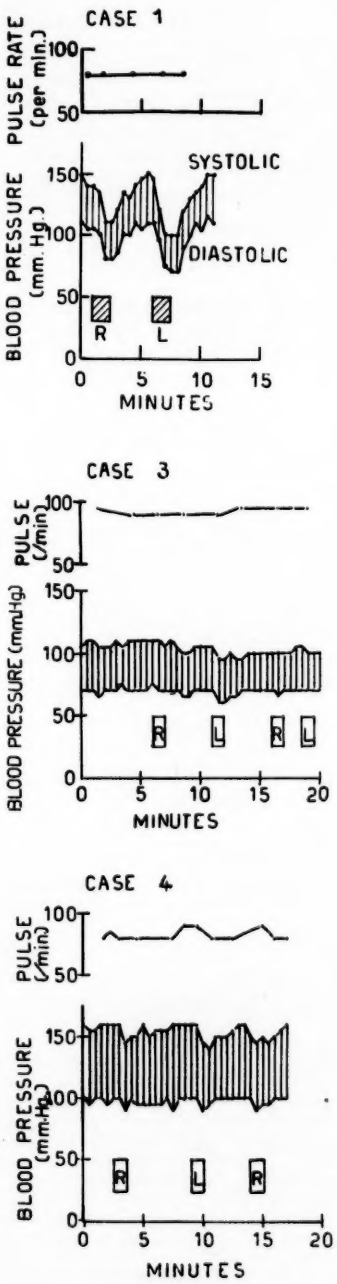

FIGURE VI

Response of blood pressure and pulse rate to carotid sinus pressure. R, right side; L, left side

pupils were small and irregular, and reacted sluggishly to light and on accommodation. The ocular fundi were normal. There was rotary nystagmus in both eyes, but no other abnormality of cranial nerve function. There was widespread disturbance of sensory function, with a band of hyperæsthesia round the costal margin, and extensive regions of impairment of pain, touch, vibration and position sense. He had extensive wasting of the muscles of the arms, hands,

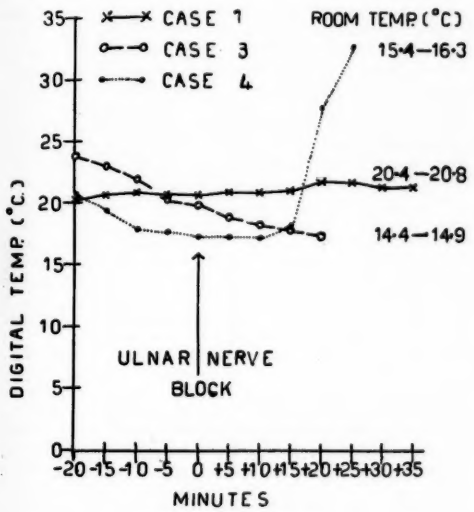

FIGURE VII

Effect on skin temperature of the fifth digit of anæsthetizing an ulnar nerve in Cases I, III and IV

thighs, calves and chest, with pronounced fasciculation, weakness and tremor. The upper limb reflexes were hyperactive, the knee jerks were normal and the ankle reflexes were absent; the superficial abdominal reflexes were normal, the plantar responses were equivocal. The Wassermann test produced a negative response in the blood and cerebro-spinal fluid. The cerebro-spinal fluid contained no cells, 90 milligrammes of protein per 100 millilitres and an increased amount of globulin. X-ray examination of the cervical part of the patient's spine revealed gross osteoarthritic changes and decalcification. Myelographic examination revealed defects from gross scoliosis, but no other abnormality.

The patient was disabled mainly by his nervous disorder and general frailty, and no treatment was given for the orthostatic hypotension.

Tests of the autonomic nervous system were not as extensive in this case as in the others, but in general the responses were similar to those in Cases I and II (Table I and Figures III to VII), indicating widespread loss of sympathetic function, with loss of vasomotor response to posture, reflex heating (at least in the hand), loss of reflex cardiac acceleration and of pilomotor activity and impairment of sweating. Lack of slowing of the pulse from carotid sinus pressure and from an infusion of noradrenaline suggested an associated parasympathetic lesion. Again, no evidence was obtained that sympathetic impulses were traversing a peripheral nerve, although there was a good response to the transmitter substance, noradrenaline. The differences in sympathetic responses between this patient and the first can probably be explained by incompleteness of the lesion.

In this patient as in the others there was a lesion of the sympathetic nervous system on the efferent side, but this time associated with other extensive neurological disorder.

CASE IV.—A woman, aged forty-eight years, complained that over the past eight years she had suffered from attacks of "dizziness" when standing—at first only in the mornings, but more recently also at other times, particularly in hot weather or when she was cooking. She obtained relief by bending her head forward. She had occasionally lost consciousness and been incontinent of urine in these attacks, but recently she had learned to prevent complete syncope by bending double at the onset of dizziness. She had failed to sweat in recent years. Over the past twelve months she had lost sexual desire; during the past six months she had become depressed and her speech had become slurred. She had suffered from

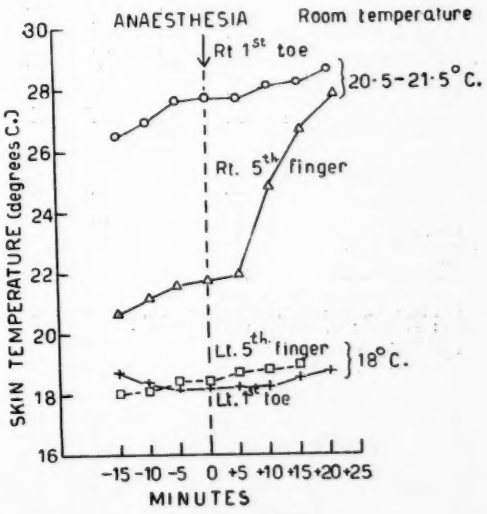

FIGURE VIII

Effect of anæsthetization of peripheral nerves in Case II. The records shown in the upper two graphs were obtained on a different day from those shown in the lower two graphs. Also, prior to the observations on the left first toe the feet were cooled by immersion in cold water

constipation over the past twenty years, and for twelve months she had had difficulty in emptying her bladder completely. Her right breast had been removed three years previously for a "fibroid growth".

The patient was a well-nourished woman with a warm, dry skin. Her heart, lungs and abdomen were normal. Her blood pressure fell considerably when she was in the erect posture so that within one minute she usually became too faint to stand; only a slight rise in pulse rate accompanied the hypotension

(Figure I). Only scant relief of the postural hypotension was obtained by applying arterial occlusion cuffs to the thighs, but moderate relief was given by a tight abdominal binder and crêpe bandages on the legs, and with these she was able to stand for nine minutes.

TABLE I

Responses to Various Tests in the Four Cases[1]

Observation	Case I	Case II	Case III	Case IV
Effect on blood pressure of:				
Erect posture	F.	F.	F.	F.
Venous trapping ..	F.	F.	N.T.	F.
Reactive hyperæmia ..	F.	F.	N.T.	F.
Exercise	F.	F.	N.T.	F.
Forced expiration (Flack, 1921)	F.	F.	N.T.	F.
Cold pressor test ..	F.	N.C.	N.C.	N.C.
Pain	F.	Sl. F.	F.	Sl. F.
Carotid sinus pressure ..	F.	Sl. F.	N.C.	F.
Noradrenaline	R.	R.	R.	Sl. R.
Relief of postural hypotension by:				
Bandaging	o	±	N.T.	±
Arterial occlusion (cuffs to thighs)	±	±	N.T.	±
Anti-gravity suits ..	±[2]	±	N.T.	+[3]
Effect on heart rate of:				
Postural blood-pressure fall	N.C.	N.C.	N.C.	Sl. R.
Pain	N.C.	N.C.	N.C.	N.C.
Exercise	N.C.	N.C.	N.T.	R.
Carotid sinus pressure ..	N.C.	N.C.	N.C.	N.C.
Atropine	N.C.	N.C.	N.T.	R.
Noradrenaline	R.	R.	R .	N.C.
Effect on blood flow of:				
Reflex hyperæmia: hand	N.C.	N.C.	N.C.	R.
Reflex hyperæmia: foot	N.C.	N.C.	Sl. R.	R.
Peripheral nerve block: ulnar	N.C.	R. (right) N.C. (left)	N.C.	R.
Peripheral nerve block: post-tibial	N.T.	N.C.	N.T.	R.
Sweating from:				
Body heating	o	o	N.T.	±
Local agents	o	+	±	+
Pilo-erection from:				
Cold	o	+	o	+
Local noradrenaline ..	++	+	+	+

[1] F., fall; R., rise; N.C., no change; N.T., not tested; o, no effect; ±, slight; +, moderate; ++, excessive.
[2] See text.
[3] See Figure IX.

No abnormality was noted in cranial nerve functions. She made little spontaneous movement, and slight weakness, in coordination and increased tone were noted in her left arm and leg. The sensory functions were normal. The tendon reflexes were brisk, the left knee-jerk being more active than the right, and the plantar responses were flexor in type.

X-ray examination of her chest and electrocardiographic examination revealed no abnormality. The hæmoglobin level was 12·1 grammes *per centum* and a blood film was normal. The blood urea level was 33 milligrammes per 100 millilitres. The patient had a mild urinary infection, which responded to treatment with sulphonamides. Of a water load of 1500 millilitres given orally, 62% was excreted in four hours. The eosinophile leucocyte count showed a normal drop after an intravenous infusion of ACTH.

The effect of the injection of various sympathetic amines (noradrenaline, ephedrine, amphetamine, methyl-amphetamine and methoxamine) was noted. In general these produced a rise in blood pressure, but did not prevent its fall when the patient was in the erect posture. However, with ephedrine, although the rise in blood pressure during recumbency was only slight, the fall on standing was greatly reduced. (It seemed that this effect resulted at least partly from an increased heart rate.) Unfortunately, when ephedrine was given orally the side effects—palpitation and nervous irritability—were very troublesome and were not prevented by phenobarbital. The patient was treated in turn by means of a "head-up" bed, extra salt, and DOCA, all without significant effect. Only slight relief of the postural symptoms was obtained by wearing tight corsets. The dramatic effect of an antigravity suit (Figure IX) has raised the hope that she may benefit from pressure clothing.

Investigations of the autonomic nervous system showed that, like the others, this patient had lost the ability to maintain a normal blood pressure in the face of change in posture, venous trapping and reactive hyperæmia, and her blood pressure did not rise from the "pressor" tests of cold immersion and pain.

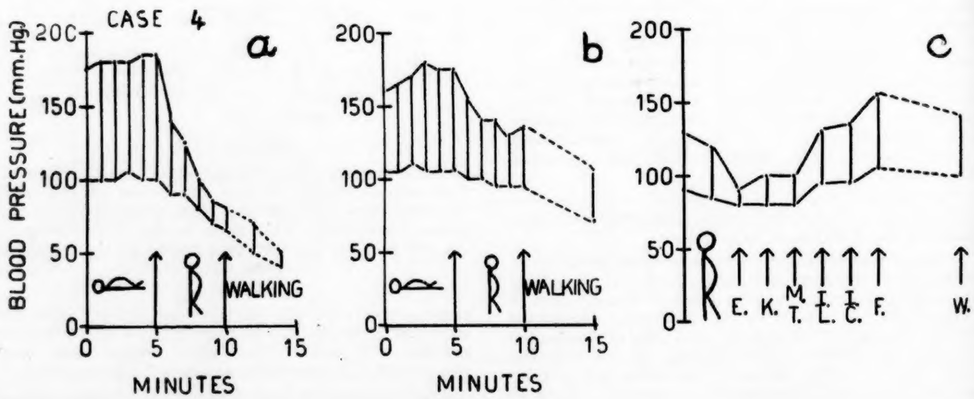

FIGURE IX

Effect on orthostatic hypotension of anti-gravity suits in Case IV: (*a*) no suit; (*b*) air-filled suit; (*c*) water-filled suit; patient standing throughout. E, empty; K, suit filled with water to knee; M.T., filled with water to mid-thigh; I.L., filled with water to inguinal ligament; I.C., filled with water to iliac crest; F, suit completely filled with water; W, after the patient had walked for five minutes with the suit filled

The blood pressure rise from infusion of noradrenaline was of normal degree only. There was only slight impairment of reflex sweating. Hyperæmia of the extremities occurred normally from reflex heating and anæsthetization of peripheral nerves. The amount of noradrenaline excreted in the urine was 20 micrograms per litre. The pulse rate rose normally on exercise. There was little change in pulse rate associated with the orthostatic blood pressure fall or with pressure on the carotid sinuses. However, the pulse rate rose after injection of atropine.

In summary, the disturbance of sympathetic nervous function involved almost entirely the reflexes controlling blood pressure, other vasomotor reflexes and sympathetic activity being relatively intact. The vessels could respond normally to the transmitter substance, and sympathetic impulses were passing along peripheral nerves. There was some evidence of slight parasympathetic nervous dysfunction. The patient had also other neurological disturbance, of the nature of degenerative Parkinsonism.

DISCUSSION

Clinical Types

Mention has already been made of the fact that orthostatic hypotension is not a single entity but may be divided into two large groups, sympathicotonic and asympathicotonic, as suggested by Nylin and Levander. A study of the reported cases and of those described in this paper indicates that the asympathicotonic group itself is not homogeneous. There is a subgroup conforming to a fairly constant pattern (with considerable orthostatic fall in blood pressure without change in pulse rate, with anhydrosis and, in males, with impotence), as exemplified by the three cases of Bradbury and Eggleston and by Cases I and II of this paper. However, even here the picture is not uniform. In certain instances, as in our Case I, the sympathetic nervous lesion is practically total. In others, as in our Case II, certain regions or functions are partially spared. The defect may vary in extent, not only from patient to patient, but also with time in the same patient. Thus in certain of the reported cases—Case II of Ghrist and Brown (1928), the case of East and Brigden (1946), the case of Rosecan *et alii* (1952)—as well as Case I of this paper, the loss of sweating was at first unilateral and later bilateral. A similar progression of the lesion may occur in that part of the sympathetic nervous system concerned in postural reflexes, so that at some stage there may be considerable loss of vasoconstrictor activity with retention of reflex tachycardia; this may be lost later, as in Case I of Verel (1951).

In addition to these apparently "primary" cases, there are others in which there is either an overt neurological disorder or some evidence of a neurological lesion on careful examination. Again, the loss of the sympathetic nervous system functions may be practically universal, or some regions or functions may be spared. In our Case III the lesion, although not universal, was widespread, and involved various sympathetic functions, whereas in our Case IV only the reflexes concerned in the regulation of blood pressure were greatly affected.

Site of Lesion

Because the distinction between the two main types of orthostatic hypotension was not appreciated until recently, the views of previous workers on the site of the lesion will only be mentioned briefly. Some authors—for example, MacLean and Allen (1940)—included both sympathicotonic and asympathicotonic types in the same report without distinguishing between them, and they believed that postural hypotension in general resulted from failure of venous return due to pooling of blood in the lower extremities.

In the fully-developed asympathicotonic type as described by Bradbury and Eggleston (1925), there is evidence of widespread disturbance of sympathetic nervous functions. These authors suggested that the lesion consisted in "paralysis of sympathetic vasoconstrictor endings". Ghrist and Brown (1928) considered that the disease represented "a hypotonic state of the myoneural structure of the sympathetic and parasympathetic system of unknown origin".

Laubry and Doumer (1932) believed that orthostatic hypotension was due to a defect in the regulator mechanism of blood pressure, probably in the "carotid sinus centre". More recently Capps and de Takats (1938) described two patients who developed orthostatic hypotension without tachycardia after operative denervation of both carotid sinuses; they suggested that some of the cases of the idiopathic variety might have a similar basis.

Stead and Ebert (1941), Jeffers *et alii* (1941), Nylin and Levander (1948) and Verel (1951) all believed that the lesion was "central".

Theoretically the lesion of the sympathetic nervous system may be in receptors, in afferent pathways outside the central nervous system, in nervous centres or their connexions, in efferent pathways outside the central nervous system, at the myo-neural junction, or in the effector cells. The parasympathetic component of the autonomic nervous system may also be involved.

Our Cases I and II were very similar, and the evidence indicated a lesion in efferent sympathetic pathways. Thus we have shown that the vessels could respond to the transmitter substance, and that there was lack of sympathetic impulses passing along peripheral nerves. Had the lesions been central there would still have been some sympathetic nervous activity from spinal reflexes. Confirmatory evidence of a peripheral lesion was given by the low excretion of noradrenaline and the hypersensitivity of some tissues to this substance. The apparent paradox of lack of sweating from locally injected noradrenaline in Case I really supports this view, because the sweat glands form an exception to Cannon's law that denervated structures are hypersensitive to the transmitter substance; in fact, they atrophy. Although Case III differs from Cases I and II in that the sympathetic dysfunction was associated with other neurological disturbances, tests indicated that again the lesion was peripheral. It is not possible to decide firmly between a lesion of nerve fibres and an inability to form noradrenaline. However, the latter is unlikely, because there was some evidence of an associated lesion of the parasympathetic nervous system, which uses a different transmitter substance—acetylcholine. We have not been able to explain certain responses, particularly the fall in blood pressure from a cold pressor test, pain, and carotid sinus pressure in Case I. Apparently painful stimulation produced certain depressor responses not subserved by the particular autonomic fibres involved in degeneration.

In Case IV, the defect involved mainly reflexes concerned with blood pressure control, and it was shown that the peripheral nerves were transmitting sympathetic impulses. The lesion must therefore be in receptors, in afferent nerves, or in central regions of the nervous system. A lesion of the carotid sinus mechanism did not seem likely in this patient, because it would not cause lack of the pressor response to cold and pain, and because the rises in blood pressure and in pulse rate expected from such a lesion (Heymans *et alii*, 1933; Samaan, 1934; Kezdi, 1953) were not present. However, there is little knowledge of the effects of chronic carotid sinus denervation in man. In the patients of Capps and de Takats (1938), the post-operative hypertension was only temporary. However, the picture in these patients was complicated in that cervico-dorsal sympathectomy had also been performed. In view of the evidence of other neurological dysfunction (degenerative Parkinson's disease) in our patient, it seems likely that a related lesion was responsible for the disturbance of both the voluntary and autonomic nervous systems. As the centre concerned in the maintenance of blood pressure is situated in the *medulla oblongata* (Wiggers, 1949), it is likely that the lesion extended to this level. (However, it could not be shown by electro-encephalography or air encephalography.)

Treatment

The sympathicotonic type of orthostatic hypotension may sometimes be cured by remedying the defect causing pooling of blood—for example, by the surgical treatment of venous angioma (Jeffers *et alii*, 1941). Otherwise the treatment of both the sympathicotonic and asympathicotonic types is similar: either to minimize the shift of blood with posture, or to increase the blood pressure, so that, although a fall still occurs in the erect posture, it is not to the level producing syncope.

Bandaging of legs and abdominal binders have been used by various workers (Cappaccio and Donald, 1938; Verel, 1951; Crost and Friedlander, 1952) without striking benefit. MacLean and Allen (1940) claimed great benefit from a "head-up" bed; Verel (1951) considered that it helped two of his three patients, Crost and Friedlander (1952) noticed no benefit in their one case. Administration of extra sodium chloride (Cappaccio and Donald, 1938; Crost and Friedlander, 1952) has been disappointing. Administration of DOCA and salt has been beneficial (Luft and Sjögren, 1948; Crost and Friedlander, 1952). The following vasoconstrictors have been used, with varying results: ephedrine (Ghrist and Brown, 1928; Korns and Randall, 1937; Cappaccio and Donald, 1952); amphetamine (Korns and Randall, 1937; Davis and Shumway-Davis, 1937; Jeffers *et alii*, 1941); "Neo-Synephrine" (Cappaccio and Donald, 1938); "Paredrine" (Jeffers *et alii*, 1941).

In our cases, the various treatments tried so far have been disappointing. The use of a "head-up" bed (in three cases) was valueless. The administration of DOCA seemed to give slight relief in Case I, but not in Case IV. One patient (Case II) is getting some relief from the use of elastic stockings. Ephedrine has not materially helped the two patients in whose treatment it has been tried. The dramatic temporary relief afforded by immersion in water and the use of antigravity suits has raised hopes that the symptoms may be controlled by the use of a pressure suit—if one can be made suitable for everyday wear.

SUMMARY

Four new cases of severe orthostatic hypotension are reported.

Investigations have been performed in order to discover the site and extent of the lesion in each case. In two there was widespread loss of autonomic nervous activity, which was the sole significant abnormality. In these, the lesion of the sympathetic nervous system was shown to lie in efferent pathways.

A third patient had similar widespread loss of autonomic nervous function associated with extensive general nervous disease. The lesion was again shown to be in efferent pathways.

In the fourth case, the disturbance of sympathetic nervous activity mainly affected reflexes controlling blood pressure. There was evidence that efferent sympathetic nervous pathways were intact, and the lesion was believed to be situated centrally in the nervous system.

The clinical types of orthostatic hypotension, the site of the lesion and the treatment of the condition are discussed.

ACKNOWLEDGEMENTS

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A COMPARISON OF PLACEBO AND HEPARIN TREATMENT IN INTERMITTENT CLAUDICATION.[1]

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SINCE no treatment of intermittent claudication in use is particularly satisfactory, any claim for a new remedy supported by reasonable evidence is worthy of consideration.

Interest in the possible effect of heparin in atherosclerosis began with the observation of Hahn in 1943 that heparin abolished alimentary lipæmia. Gofman and his colleagues (Graham *et alii*, 1951) gave heparin to patients with coronary sclerosis in an attempt to remedy the abnormal pattern of plasma lipoproteins which they had previously reported in this condition (Gofman *et alii*, 1950) and observed incidentally that most of the patients in their series who suffered from *angina pectoris* obtained speedy relief. Subsequently Engelberg (1952) confirmed that heparin was beneficial in *angina pectoris*. Others (Rinzler *et alii*, 1953; Grüner *et alii*, 1953; Chandler and Mann, 1953) stated that it was not superior to a placebo.

After his favourable experience with heparin in *angina pectoris*, due to coronary atheroma, Engelberg tried its effect in the analogous condition of intermittent claudication, due to atheroma of the arteries of the lower limbs, again with good results (Engelberg and Massell, 1953); with the intramuscular injection of 100 milligrammes of heparin two or three times a week for several months, the walking distance of seven out of ten patients increased considerably. However, Grüner and his associates (1953) noted improvement in only one of five patients with intermittent claudication treated with heparin.

After reading Engelberg and Massell's report, we gave heparin to A., a man, aged fifty years, who had suffered from progressive intermittent claudication for two years and found that he obtained considerable benefit: within ten weeks of the commencement of treatment, his walking distance, according to his estimate, had increased from five hundred to one thousand yards. His subjective improvement was accompanied by increased performance in our standard step-test (Figure I). This finding was particularly surprising since arteriography had shown complete occlusion of his femoral artery for several inches. However, the symptomatic effect in this patient was so great that we decided that the treatment should be given a serious trial.

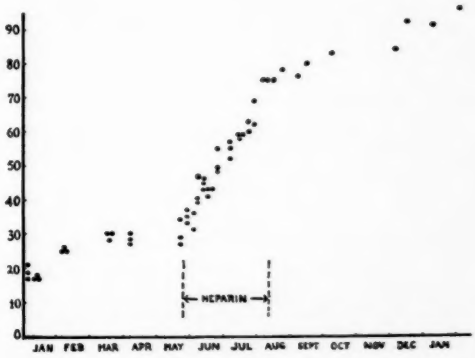

FIGURE I

Progressive improvement in step-test performance of patient A during heparin administration. The numbers are " claudication numbers " as described in the text

We had previously observed that considerable variation might occur in the severity of intermittent claudication in the absence of any treatment and that spontaneous improvement was particularly common in patients with recent onset of symptoms. We appreciated that many treatments for this condition advocated with enthusiasm in the past were later discarded as useless, and that a recent controlled study (Hamilton and Wilson, 1952) had failed to substantiate the claims for many of the currently used drug treatments. We therefore decided to study the effect of the new treatment only in patients who had intermittent claudication of considerable duration, and to precede heparin therapy by a course of placebo similarly administered.

[1] Received on May 12, 1955.

[2] George Merriman Research Fellow.

MATERIAL

Brief clinical details of ten patients studied are shown in Table I. There were nine men and one woman (Case VI). All had typical intermittent claudication in the calf, of at least six months' duration, due to *atherosclerosis obliterans*. All had clinical evidence of occlusion of a large artery, in some instances confirmed by arteriography. Some had been treated previously by other methods without benefit.

TABLE I

Clinical Details of the Patients Tested.

Case Number	Age (Yrs.)	Patient's Estimate of Walking Distance (Yards)	Duration of History of Claudication	Progress Prior to Commencement of Trial	Other Diseases
I	62	200	2½ years	Deterioration	—
II	48	300	9 months	Steady	*Diabetes mellitus*
III	73	100	6 months	Deterioration	—
IV	74	100	3½ years	Deterioration	—
V	58	500	7 months	Steady	—
VI	63	"5 minutes"	6 months	Deterioration	*Diabetes mellitus*
VII	65	100	6 months	Steady	—
VIII	64	100	2 years	Deterioration	—
IX	63	100	12½ years	Steady	Coronary occlusion one year earlier
X	63	150	5 years	Deterioration	Mild varicose veins. Prostatomegaly

METHOD

Each patient attended weekly at approximately the same hour, and after resting for half an hour in a room with a temperature of about 23° C., was asked to walk over two nine-inch steps (Master, 1942) until he first experienced the pain which had caused him to seek advice. The number of circuits over the steps ("claudication number") and the time taken were noted. This test was performed three times with intervals of at least five minutes. Longer rest periods were used when the second or third step-test showed consistently, by its diminished claudication number, that the patient had not adequately recovered from the preceding exercise. Patients were encouraged to walk at the same pace in all tests.

As a control, step-tests were repeated at intervals of one week for one to three months, and the patients were then given bi-weekly intramuscular injections of water coloured to resemble our solution of heparin. This was continued for three weeks or more (until it appeared that any improvement in performance in the step-test had ceased), and then, unknown to the patient, the placebo was replaced by heparin (10,000 units), the latter treatment being continued for three months in five cases and longer in the other five.

At various stages of the investigation the patients were asked to estimate their walking distance and to give their opinion concerning any change in their condition.

RESULTS

The results for one particular patient (Case III) are shown graphically in Figure II, and the results for the 10 patients are summarized in Table II.

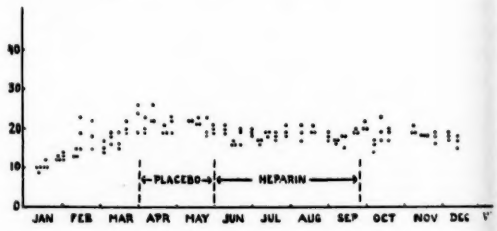

FIGURE II

Weekly step-test performances of patient in Case III recorded as "claudication numbers" (ordinate) during a twelve-months period (abscissa). The duration of treatment with placebo and heparin are shown

The scatter in step-test results varied considerably both between patients and between tests on the same patient on different days.

The magnitude of the scatter can be appreciated from the standard deviations listed in Table II, where the claudication numbers are the means of nine successive step-test results—those of the first three visits, those of the last three on placebo and those of the last three of the three months' heparin course.

Eight patients showed significant improvement during observation and administration of the placebo; in four cases (III, VI, VIII and X) this occurred mainly during the observation period, in the other four (Cases II, IV, V and VII) mainly during the administration of the placebo. However, as some patients regarded the mere performance of the tests as a form of treatment, we have combined observation and placebo periods in assessing the placebo effect. Because the duration of observation and placebo administration varied

TABLE II

The Response of Claudication to Therapy. The Claudication Number is the Number of Circuits Over the Steps Before the Production of Pain

Case Number	Duration of Observation and Placebo Period (Months)	Claudication Number (Mean ± Standard Deviation)			Improvement in Claudication Number[1]		
					During Observation and Placebo Period		During Three Months' Heparin Treatment
		Initial (x)	At End of Placebo (y)	At End of Three Months' Heparin Therapy (z)	($y-z$)	Per Three Months	($z-y$)
I	3	16·1±2·8	17·7±2·1	20·1±2·9	(1·6)	1·6	(2·4)
II	6	22·0±2·8	31·2±4·1	29·8±6·0	9·2	4·6	(−1·4)
III	5	11·0±1·5	20·6±1·7	17·7±1·6	9·6	5·8	−2·9
IV	4	14·0±1·7	15·8±1·0	17·6±1·1	1·8	1·4	1·8
V	7	32·3±4·4	39·8±5·7	41·9±9·2	7·5	3·2	(2·1)
VI	5	14·0±2·1	18·8±3·0	23·8±3·3	4·8	2·9	5·0
VII	2	12·7±1·8	20·7±7·4	24·3±1·7	8·0	12·0	3·6
VIII	13	14·9±5·2	24·6±1·4	27·6±2·2	9·7	2·2	3·0
IX	4	11·1±1·5	11·3±0·8	14·9±0·6	(0·2)	0·2	3·6
X	3	14·7±2·9	23·3±4·4	26·0±4·8	8·6	8·6	(2·7)

[1] Figures in parentheses are not significant ($P>0·05$).

from patient to patient, this effect is also expressed as improvement per three months (it is not implied that such improvement necessarily occurred at a constant rate).

During treatment with heparin five patients improved, one deteriorated and four showed no significant change. However, only one patient (Case IX) received much more benefit from heparin than from observation and the placebo, and, in general, the improvement during heparin therapy was not as great as that which preceded it.

Six of the eight patients whose step-test performance improved with observation and the placebo believed that they had benefited in their walking; two (Cases IV and VI), whose improvement was slight, did not notice any change in their walking distance. At the end of three months' heparin treatment, four patients thought that they had improved, six that they had not improved. However, in individual cases, the patient's estimate of his walking distance and his assessment of his condition often disagreed with the step-test performance. There was a striking lack of correlation between patients' assessments of their progress and their estimates of their walking distance: they sometimes gave widely differing estimates, yet thought their condition unchanged; on the other hand, one man (Case V) reported that he had benefited considerably and his walking distance had increased to 300 yards, when our records showed that his initial estimate had been 500 yards.

DISCUSSION

Many difficulties and fallacies are involved in assessing the effect of treatment on a symptom which, of course, can be experienced only by the patient himself. In this trial, when patients have attempted a quantitative evaluation of their complaint, internal inconsistencies have become evident. Though this occurs only with some persons, yet it invalidates any attempt to assess the benefit of treatment in intermittent claudication by only the patients' subjective estimates of walking distance. It is essential to use an objective method, and several such methods exist: for example, Boyd (1949) asks the patient to walk on an endless belt until arrested by pain. The fact that patients experience the same pain when walking over the Master steps as in normal walking indicates that the same muscles are being used (albeit in a different pattern), and therefore the step-test is a satisfactory method for judging the severity of claudication. Whatever method is used, it is important to take as end-point the first appearance of pain, rather than the point at which it becomes unbearable, because the former is probably less subject to influence by psychological factors. Moreover, the variation in step-test performance shows that single determinations may be misleading.

Spontaneous improvement in intermittent claudication due to a recent arterial occlusion is often observed, and the symptom may practically disappear. However, improvement without specific therapy may occur in claudication which has been present for several years, as instanced by our Cases VIII and X. Even more dramatic cases are seen. For example, a man, aged sixty-two years, who for twelve months had intermittent claudication due to radiographically demonstrated occlusion of the external iliac artery, reported after a six-month interval that his walking distance

had increased from 50 to 500 yards; his claudication number by the step-test had increased from 15 to 60.

It is obvious that in this condition a pre-treatment observation period is essential, unless a "double-blind" controlled investigation is planned. We have used a sequential method for reasons of economy in patient material. It was anticipated that each patient would act as his own control. However, the benefits of observation and the administration of placebo were greater than anticipated. Lasagna *et alii* (1954) claimed that some people are more prone to react favourably to a placebo than others, and that such "placebo-reactors" can be recognized by psychological testing. An undue proportion of placebo reactors in a clinical trial may mask any real, specific, effect of the test substance. This may have happened in our trial, and it may be argued that heparin failed to prove of much benefit because maximal improvement had already been elicited in suitable subjects by the placebo. However, a remedy for intermittent claudication need hardly be considered of practical value unless its effects are of considerable magnitude and greater than those of a placebo. If heparin did fulfil these conditions, one would have expected it to elicit considerable improvement at whatever stage in a trial it was used. The benefit of heparin administration in our preliminary case (Figure I) and in the study of Engelberg and Massell (1953) cannot be attributed to any specific action, since no placebo control was used.

The magnitude of placebo effects is being appreciated only now (Leslie, 1954). Many still hold that a favourable response to a placebo indicates, if not malingering, at least that the symptom is hysterical. Yet a number of published articles and the experience of many clinicians attest to the effects of a placebo in organic conditions. Diehl and his colleagues (Diehl *et alii*, 1940; Cowan *et alii*, 1942) reported a reduction in incidence of the common cold from five or six a year to two in several hundred students given a placebo. Beecher *et alii* (1953) obtained relief of post-operative pain by a placebo in over 40% of patients. Wolf (1950) observed hyperæmia and hyperacidity in the herniated gastric mucosa of his patient, Tom, when he was given a placebo, and he was actually able to reverse the pharmacological effect of atropine by suitable psychological conditioning. The same worker (Wolf, 1953) later reported toxic reactions, a maculo-papular rash, angioneurotic œdema and diarrhœa, following the administration of a placebo. Dunbar (1939) lists numerous references concerning the effect of suggestion on bodily functions. Great improvement in intermittent claudication from placebo treatment is illustrated in our Cases II and VII. Even more striking improvement from a placebo is sometimes seen, as instanced in the case of a man, aged seventy years, with intermittent claudication in the right leg and foot of three years' standing, due to occlusion of the whole femoral artery (demonstrated by angiography) and a walking distance of 200 yards, who was given nine injections of saline or glucose solution into his femoral vein at weekly intervals; at the end of this time he said he could walk indefinitely on level ground without suffering pain in the calf; his claudication number had improved from an initial 20 to 45.

Summary

After a preliminary period of observation and placebo administration, 10 patients with intermittent claudication in the calf were given bi-weekly intramuscular injections of heparin (10,000 units). Results were assessed on the patient's performance in a standard step-test.

Eight patients benefited by mere observation and the administration of a placebo. Only one patient derived more benefit from heparin than from the preceding placebo treatment.

The difficulties in assessing the effect of treatment in intermittent claudication are discussed, and evidence is produced to show that the condition may undergo spontaneous relief.

The powerful effects of placebo therapy in this condition are discussed.

Acknowledgements

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CHANGES IN THE HEART IN DYSTROPHIA MYOTONICA.[1]

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Dystrophia myotonica (*myotonia atrophica*, or myotonic dystrophy) is a heredo-familial disorder which affects males and females alike and is transmitted by both sexes. When the disease first makes its appearance in a family, cataract is usually the only sign. In the second generation the cataract develops at an earlier age and the features of the fully developed disorder appear—muscle wasting, myotonia, frontal baldness, bony changes in the skull, cardiac abnormality, physical and mental defects and certain endocrine changes of which cataract and gonadal atrophy are the most constant. In the third generation the fully developed disorder may be present in childhood with associated mental or physical defects; but either mental or physical defects or both may be the only evidence of the disease. From a previous study of *dystrophia myotonica*, one of us (J.E.C.) has previously reported on the cataract (1933), the endocrine changes (1950, with Brown), the changes in the skull (1952), the unilateral elevation of the diaphragm (1954, with Gray) and the occurrence of congenital physical defects in affected families (1954, with Barclay). The object of this paper is to describe the cardiac changes we have encountered in some of these patients whose histories have been previously reported, and in others investigated in New Zealand in the past ten years.

HISTORICAL BACKGROUND

Myotonia was first described by Leyden (1874), and in 1875 Thomsen recorded in detail the myotonia from which he himself suffered. The association of myotonia and muscle atrophy was first described by Dana (1888). Batten and Gibb (1909) and Steinert (1909) recorded details of the fully developed disorder, and first described changes in the mental state, premature frontal baldness and gonadal atrophy. At the time these last-mentioned findings were regarded as being merely coincidental, but in 1911 Greenfield recorded the association of cataract with the disorder, and thereafter the other dystrophic manifestations came to be recognized as variable features of the clinical picture.

Probably the first reference to the heart in *dystrophia myotonica* was made by Griffith (1911), who described the case of a male subject, aged forty-eight years, with bradycardia (his heart rate was 36 per minute), but no heart block. Maas and Zondek (1920) reported three cases in which they found a dilated heart and an increase in the *P-R* intervals. Guillain and Rouques (1932) reported prolongation of the *P-R* or *QRS* intervals in three out of five cases. Curschmann (1925) reported one case in which the *P-R* intervals varied from 0·27 to 0·29 second. Biork (1944) reported four cases in which there were abnormal electrocardiograms and a prolongation of the *P-R* and *QRS* intervals, and in one a prolongation of the *P-R* interval was associated with transitory auricular flutter. Evans (1944) reported 13 cases, in all of which the *P-R* interval was 0·2 second or more. Fisch (1951) has reviewed the literature and reported five cases in which the electrocardiograms were abnormal. From the literature he found that 85 patients had had electrocardiographic studies, and 68% of these had abnormal tracings. This may give a false impression of the incidence of abnormalities in the electrocardiogram, as many authors would report only the abnormal examples. Waring, Ravin and Walker (1940) indicate that the blood pressure in these patients is practically never raised.

Both enlarged and diminished radiological cardiac shadows have been reported by Harvier and Decourt (1933), by Londres (1935) and by Evans (1944), but usually the heart size is normal. Evans reports defective heart tone in 10 out of 13 patients. Thomsen has stressed that cardiac symptoms are rare.

Histological examination of the heart muscle in the few reported autopsies has not shown any of the changes of the type seen in skeletal muscle (Adams, Denny-Brown and Pearson,

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[2] In receipt of a grant from the Dunedin Branch of the Crippled Children's Society of New Zealand.

1953). However, Londres (1935) did think the histological picture of the myocardium presented changes similar to those in the striated musculature.

CLINICAL MATERIAL

In the past ten years we have had the opportunity of studying 35 subjects of *dystrophia myotonica* with the fully developed disorder. In 18 of these we were able to study the cardiovascular system, some in more detail than others. A brief account of the clinical findings without laboratory investigation will be presented except for the details of the electrocardiographic findings, which are summarized in Table I.

CASE RECORDS

CASE 1.—D.G.H., an unmarried panel-beater, aged twenty-six years, had noticed difficulty in relaxing his grip and progressive wasting of his limbs for two years. In 1945 he developed palpitations and breathlessness and was admitted to hospital, where an electrocardiographic examination revealed auricular flutter. He had a myopathic facies, ptosis and wasting of the anterior cervical muscles, forearms and legs. There was active myotonia of the grip and mechanical myotonia of the tongue and muscles of the

TABLE I

Case Number	Patient's Sex and Age (Years)	Rhythm	*P-R* Interval (Seconds)	*QRS* Voltage	Duration of *QRS* Complex (Seconds)	*Q-T* Interval	*T* Waves and *S-T* Segment	Blood Pressure (Millimetres of Mercury)[1]
1	M, 26	Auricular flutter 8 : 1 or 4 : 1 auricular-ventricular block. Restored to sinus rhythm with quinidine	(Later) 0·17	Normal	0·04	Normal	Normal	115/85
2	F, 45	Sinus	0·16	Normal	0·05	Normal	*S-T* segment elevated in leads I and II	150/75
3	F, 51	Sinus	0·22	High	0·130 (left bundle branch block)	Upper limit of normal	*T* wave upright in leads I and V_2	—
4	M, 28	Sinus	0·16	Low in leads V_1 to V_2	0·06	Normal	Normal	105/80
5	M, 41	Sinus. Episodes of sino-auricular block	0·24	High	0·16 (left bundle branch block)	Normal	*T* biphasic in lead I	100/55
6	M, 33	Sinus	0·16	Normal	0·09	Normal	*S-T* elevated in leads II and III	110/70
7	F, 42	Sinus. Ventricular ectopic beats	0·20	High	0·125 (left bundle branch block)	Slightly prolonged	*T* upright in lead I	—
8	F, 58	Sinus	0·18	Normal	0·08	Slightly prolonged	*T* wave low in aV_L and all standard leads	118/72 (184/130) in failure)
9	M, 29	Sinus	0·16	Normal	0·07	Normal	Normal	104/70
10	M, 36	Sinus	0·17	Normal	0·07	Normal	*S-T* segment elevation in leads V_6 and aV_F	105/50
11	F, 51	Sinus. Ventricular ectopic beats	0·18	Grossly increased	0·12 (Arborization block)	Slightly prolonged	Normal	130/90
12	M, 19	Sinus	0·20	Normal	0·08	Upper limit of normal	*S-T* segment elevation in leads V_2 and V_3	120/80
13	M, 51	Sinus. Ventricular ectopic beats (*R* on *T* wave phenomenon)	0·22	Normal	0·08	Normal	*S-T* segment elevation in leads V_2, V_6 and aV_F, and in lead III)	110/90
14	M, 42	Sinus	0·22	Normal	0·06	Normal	Normal	115/80
15	M, 46	Sinus	0·16	Normal	0·04	Upper limit of normal	*S-T* segment elevation in leads V_2, V_6 and aV_F	106/85
16	F, 40	Sinus	0·16	Normal	0·08	Normal	Normal	112/70
17	F, 40	Sinus	0·16	High	0·07	Long normal	Normal	115/80
18	F, 29	Sinus	0·22	Slightly low	0·06	Normal	Normal	110/65

[1] Systolic/diastolic

hands. The deep reflexes were uniformly reduced. X-ray examination of the skull revealed a *hyperostosis frontalis interna*. He was treated with quinidine in increasing dosage, which completely relieved the myotonia and caused the heart to revert to a normal sinus rhythm.

CASE 2.—F.M., an unmarried pensioner, aged forty-five years, had noted difficulty in relaxing his grasp for thirty-two years and wasting and weakness of his limbs for twenty-seven years. His vision had deteriorated steadily for thirty-two years. He had bilateral cataracts and a myopathic facies with ptosis, and wasting and weakness of the cervical muscles and of the arms and legs. Active and mechanical myotonia was present. When he had been originally examined at the age of thirty-six years, the cardio-vascular system was normal. The blood pressure was 150 millimetres of mercury, systolic, and 75 millimetres, diastolic. At the age of forty-one years, an aortic diastolic murmur was present, but the heart was of normal size. In 1950, at the age of forty-six years, besides the murmur there was reduplication of both first and second sounds. The electrocardiogram was normal. The heart size remained normal on X-ray examination; the response to the Wassermann test was negative, and there was no congestive heart failure up to the time of his death brom bronchopneumonia in that year. At the post-mortem examination, the superficial surface of the heart showed a moderate degree of fibrosis. No abnormality of cardiac muscle was detected on examination of sections, and the aorta appeared normal.

CASE 3.—E.B., a married woman, aged fifty-one years, had noticed weakness of her neck muscles at the age of thirty years, and wasting and weakness of her forearms and legs for five years. For several years she had noticed difficulty in relaxing her grip when wringing the clothes. Her only son was mentally defective and had *dystrophia myotonica*. Her speech was slurred, and she had a myopathic facies, ptosis, and wasting and weakness of the anterior cervical muscles, the forearms and the legs. Active and mechanical myotonia of the thenar muscles was present. She had bipolar cataracts. She had considerable thickening of the calvarium with *hyperostosis frontalis interna* and a small pituitary fossa. The cardio-vascular system was normal apart from a left bundle branch block revealed in the electrocardiogram.

CASE 4.—J.B. was an unmarried pensioner, aged twenty-eight years, whose mother (Case 3) had fully developed *dystrophia myotonica*. He was backward at school, and at the age of sixteen years he noticed difficulty in relaxing his grip, and in the following year weakness of his limbs. His vision was failing. His speech was slurred, he had bilateral lenticular opacities and a myopathic facies with ptosis. The forearms and legs were wasted, and there was active myotonia of the grip and mechanical myotonia of the tongue and small muscles of the hands. The knee and ankle jerks were not elicited. His testes were small and soft. He had pronounced radiological changes in the skull, with hyperostosis, thickening of the calvarium and a small *sella turcica*. He was dull and his intelligence quotient was 74. The cardio-vascular system was normal apart from the electrocardiogram, which showed an absence of *R* waves in leads V_1 to V_3 with deep *S* waves in these leads.

CASE 5.—C.C.W., an unmarried carpenter, aged forty-one years, had noticed loss of potentia at the age of thirty-four years, and four years later complained of difficulty in relaxing his grasp, of weakness and wasting of his forearms and legs and a tendency to fall. He was a bald, wasted man with a myopathic facies and wasted neck muscles, and his forearms and legs were wasted and weak. His speech was slurred. He had pronounced active and mechanical myotonia. All the deep reflexes were absent. His testes were small and soft. A number of cardio-vascular abnormalities were found. The pulse rate was 50 per minute, the apical second sound was reduplicated, and an electrocardiographic examination revealed first degree heart block, episodes of sino-auricular block and left bundle branch block.

CASE 6.—F.S., an unmarried grocer, aged thirty-three years, who had been backward at school, had first noticed myotonia at the age of thirteen years, and at fifteen years he developed weakness and wasting of his limbs which progressed. He was a thin, dull-witted man with a myopathic facies and wasted limbs, and pronounced myotonia of his grip and mechanical myotonia of his tongue and thenar eminences. His pituitary fossa was very small. The cardio-vascular system was normal apart from electrocardiographic changes of a minor nature. At the post-mortem examination no abnormality was seen in the heart either macroscopically or microscopically.

CASE 7.—M.J.S. was a single woman, aged forty-two years, who had noticed difficulty in relaxing her grip for three years; eighteen months later she had developed weakness and wasting of her forearms and legs and begun having frequent falls. She was mentally defective and had been in a mental hospital for nine years. She was poorly nourished and had a myopathic facies, wasting of her neck and limbs and pronounced myotonia of the tongue and grip. She had bilateral cataracts. Radiographic examination of the skull revealed hyperostosis and a small pituitary fossa. The heart was not enlarged and the heart sounds were normal, but the electrocardiogram revealed an unusual type of left bundle branch block.

CASE 8.—L.F., a married woman, aged fifty-eight years, was admitted to hospital on account of weakness, breathlessness and lassitude present for three months, and a persistent unproductive cough. On investigation she was found to have *dystrophia myotonica*. She had noticed difficulty in relaxing her grasp and progressive weakness for several years. She had been subject to many falls. She had a myopathic facies and weakness and wasting of the anterior cervical muscles, the forearms and legs. The ankle jerks were absent and she had active and mechanical myotonia. Both lungs were congested, but there was no elevation of the jugular venous pressure and no peripheral œdema. The blood pressure was 184 millimetres of mercury, systolic, and 130 millimetres, diastolic. The heart was slightly enlarged, the apex beat was in the fifth intercostal space one inch beyond the mid-clavicular line, and radiologically this enlargement was thought to be mostly right-sided. Dilatation and unfolding of the aorta were also present, with early calcified atheromatous changes in the aortic arch. The radiological appearances of the lungs showed prominence of the pulmonary arteries, with congestive changes and suggested pleural effusion at the base of the left lung. The heart sounds were normal, but there were bilateral basal rales. This mild congestive heart failure cleared up with rest alone; within six days the blood pressure was normal and remained persistently at or below 120 millimetres of mercury, systolic, and 80 millimetres, diastolic, until her discharge from hospital. The electrocardiogram showed no distinct abnormality, although in lead aV_L the *R* wave was rather tall and wide and the *T* wave on the low side of normal.

On the patient's further admission to hospital in March, 1952, there were again signs of minimal heart failure, but the main condition was one of bronchitis, which had been present for a month. There were numerous ventricular ectopic beats. The first sound was split at the lower sternal region. There were no changes in the heart size on X-ray examination, and the lung fields were clear. An electrocardiogram showed abnormally tall *R* waves over the left ventricle with iso-electric *T* waves, and ventricular ectopic beats. The blood pressure was 130 millimetres of mercury, systolic, and 74 millimetres, diastolic, in the left arm, and 118 millimetres of mercury, systolic, and 72 millimetres, diastolic, in the right arm. (Following admission there was no manifest return of congestive heart failure.) The patient had no digitalis therapy.

CASE 9.—R.F., a married pensioner, aged twenty-nine years, was admitted to hospital on account of a cough and hæmoptysis, and was found to have a primary atypical pneumonia syndrome probably influenzal in origin. He was also found to have fully developed *dystrophia myotonica* with typical wasting, myotonia and diminished deep reflexes. There were no symptoms or signs referable to the cardio-vascular system. The electrocardiogram was within normal limits.

CASE 10.—A.F., an unmarried labourer, aged thirty-six years, had been well until the age of fourteen years, when he noticed difficulty in relaxing his grip. Two years later he noticed loss of strength first in his right arm, then in his left arm and in the calves. Wasting in his forearms and legs then began. He had weak facial muscles and bilateral ptosis. On slit lamp examination he was found to have bilateral lenticular opacities. He had wasting and weakness of the sterno-mastoid muscles, the forearms and the legs. Dorsiflexion of the feet was very weak. There was active and mechanical myotonia, the knee jerks were depressed and the ankle jerks were lost. His testes were small and soft. He complained of some exertional dyspnœa, but the heart was normal on gross examination and on fluoroscopic screening. The electrocardiogram showed no abnormality apart from a concave elevation of the *S-T* segment in lead V_6 and in lead aVF of approximately one millimetre. Test doses of quinine (15 grains) and "Prostigmine" (2·5 milligrammes) did not alter the appearance, and potassium given by mouth increased the voltage of the *T* wave but did not affect the S-T segment level.

CASE 11.—J.M., a married housewife, aged fifty-one years, had been well until the age of forty-seven years, when she became weak at the knees. A year later she commenced having falls at unexpected times and had difficulty in rising once she had fallen. For some time she had noticed difficulty in relaxing her grasp. She had bilateral lenticular opacities, and wasting of the anterior cervical muscles, the forearms and of the lower extremities. There was mechanical myotonia of the tongue and thenar muscles and mechanical myotonia of the grip. The deep reflexes were all lost. There were no symptoms or signs referable to the heart, but the electrocardiogram was abnormal, showing a pronounced arborization block and ventricular ectopic beats.

CASE 12.—R.F., an unmarried mill hand, aged nineteen years, had been backward at school, and for a few years had noticed difficulty in relaxing his grip in cold weather. There was no evidence of muscle weakness or wasting, but he had mechanical myotonia, pronounced in the tongue and small muscles of the hands, and active myotonia of the grip. There were no symptoms referable to the cardio-vascular system, but the electrocardiogram revealed bizarre *QRS* complexes in the unipolar limb leads and elevation with an upward concavity of the *S-T* segment in leads V_2 and V_3.

CASE 13.—P.S., an unmarried pensioner, aged fifty-one years, had first noted slurring of his speech thirty-eight years earlier, weakness and difficulty in relaxing his grip twenty years earlier, and increasing weakness and failure of vision for six years. He had pronounced weakness and wasting of his facial muscles, ptosis, and wasting and weakness of the anterior cervical muscles, the forearms and legs. He had bilateral polar cataracts and gonadal atrophy. In spite of frequent and severe attacks of bronchitis and bronchopneumonia no congestive heart failure was observed, although a gallop rhythm was heard on one occasion. There were no symptoms referable to the cardio-vascular system. The electrocardiogram revealed a grossly abnormal elevation with an upward concavity of the *S-T* segment over the left ventricle. Frequent ventricular ectopic beats were also present. An impression was gained that the *S-T* elevation had been less on a previous occasion when the patient was taking quinidine, 18 to 24 grains per day.

CASE 14.—H.D.T., an unmarried pensioner, aged forty-two years, had noticed weakness and wasting of his neck, arms and legs for several years. He could not say at what age these symptoms had first developed. He had a myopathic facies with pronounced ptosis and weakness and wasting of the anterior cervical muscles, the arms and the legs. He was unable to sit up with his arms folded. He had pronounced active and mechanical myotonia and bilateral cataract. There were no symptoms referable to the cardio-vascular system. The electrocardiogram showed a *P-R* interval of 0·22 second.

CASE 15.—W.N.T., an unmarried pensioner, aged forty-six years, had noticed difficulty in relaxing his grip for many years, weakness and wasting of his limbs for twenty years and progressive failure of vision for eight years. He had a wasted myopathic face, and wasting of the sterno-mastoid muscles and of the muscles of the forearms and legs. He had pronounced active and mechanical myotonia, and all deep reflexes were lost. The penis was small and the testes were soft and small. He had no symptoms referable to his heart, but the *S-T* segment was elevated in the electrocardiogram.

CASE 16.—E.P.C., a married woman, aged thirty-nine years, was found to have fully developed *dystrophia myotonica* in the course of a family investigation. For twelve years she had noticed wasting and weakness of her limbs and difficulty in relaxing her grip. She had a wasted face and pronounced weakness of the flexors of the head and trunk and wasting of the neck and limbs. The ankle jerks were not obtained. She had bilateral cataracts. There were no symptoms referable to the cardio-vascular system and the electrocardiogram was normal.

CASE 17.—E.W., a spinster, aged forty years, was found to have *dystrophia myotonica* when in hospital for treatment of a subacute obstruction. She had bilateral cataract and pronounced active and mechanical myotonia. There were wasting and weakness of the facial muscles, the forearms and the legs. All the deep reflexes were lost. There were no symptoms or signs of abnormality of the cardio-vascular system. The electrocardiogram was normal.

CASE 18.—M.J., a married woman, aged twenty-nine years, reported to her doctor on account of failing

vision of five years' duration, and was found to have myotonia, which she said she had had for as long as she could remember. She had wasting and weakness of the face, forearms and legs, active and mechanical myotonia and bilateral cataract. Clinically the cardio-vascular system was normal apart from prolongation of the *P-R* interval.

TABLE II

Analysis of Electrocardiographic Findings in 18 *Cases of Dystrophia Myotonica*

Electrocardiographic Findings	Number of Cases
Normal tracings	4
Abnormalities of rhythm:	
Auricular flutter	1
Ventricular ectopic beats[1]	3
Abnormalities of conduction:	
Sino-auricular block	1
First degree heart block (*P-R* interval more than 0·2 second)	5
QRS delay (left bundle branch block, atypical pattern, 3; arborization block, 1)	4
Q-T prolongation (upper limit of normal, 4; slightly prolonged, 3)	7
S-T segment elevation with upward concavity	6
Low *T* waves	1

[1] In one case, with *R* waves on *T* waves.

RESULTS AND DISCUSSION

Of 18 cases of *dystrophia myotonica* in which a full cardiological examination was completed, in two distinct signs of abnormality were found

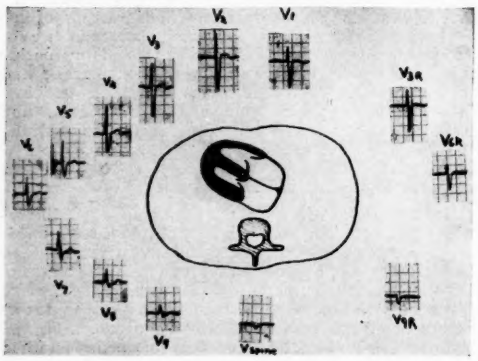

FIGURE I

Case 11. V leads recorded around the chest, *QRS* is prolonged, the delay probably being maximal in the *R* wave of V_5—that is, in the posterior wall of the left ventricle. Note upright *T* wave and absence of *Q* waves

on clinical examination, and in 14 electrocardiographic changes were present. These changes are recorded in Table I, and a summary of the findings is given in Table II.

The clinical abnormalities consisted of congestive heart failure in one case (Case 8), of which a summary is given in the foregoing case reports. In this instance none of the

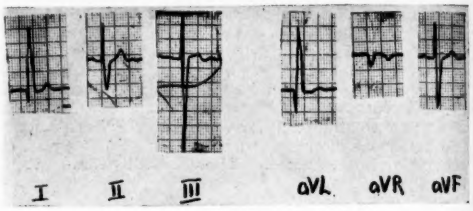

FIGURE II

Case 11. Standard leads and unipolar limb leads. Note *QRS* delay, deep *Q* wave in leads I and aVL and upright *T* waves in leads I, aVL and aVF

usual cardiac causes for congestive failure could be identified. It is notable that on the patient's admission to hospital there was a mild elevation of blood pressure, which returned to normal when the acute phase of breathlessness had passed. Since her recovery from this illness the patient has suffered from a persistent cough

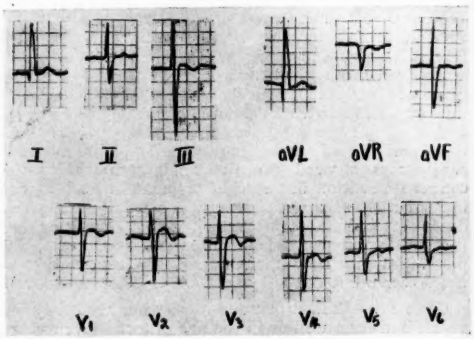

FIGURE III

Case 11. Leads I, II and III, aVL, aVF and V_1 to V_6 after ten days' quinine therapy (10 grains three times a day), which relieved the myotonia. Note *S-T* segments of leads V_2 to V_4

without sputum, and from breathlessness, both of which have been relieved from time to time by rest in bed and an occasional injection of mersalyl.

Another patient (Case 2) showed the development of aortic regurgitation toward the end of life. There was no history of rheumatic fever or of syphilis, and the blood gave a negative response to the Wassermann test. Furthermore, at the post-mortem examination no abnormality

was found at the aortic valve or in the cardiac muscle; from this it seems likely that the regurgitation was of a functional nature, probably associated with stretching of the aortic valve ring.

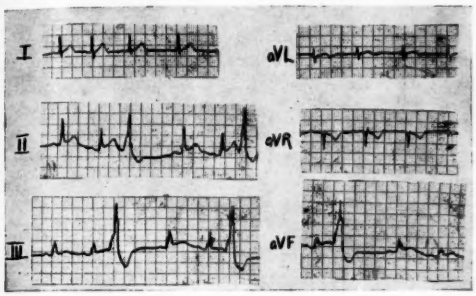

FIGURE IV

Case 13. Electrocardiogram taken on May 16, 1952, leads I, II, III, aVL, aVR and aVF. Note *S-T* segment elevation in leads II, III and aVF. There are ventricular ectopic beats showing, in lead III and in lead aVF interruption of *T* waves by succeeding *R* waves

The most striking electrocardiographic abnormality was conduction delay, presenting as a first-degree heart block in five of the cases and as bundle branch block in three, with one further case of arborization block. Figure I shows a diagrammatic section of the chest

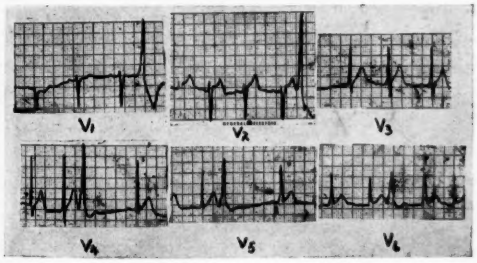

FIGURE V

Case 13. Electrocardiogram taken on June 15, 1952, leads V_1 to V_6. Note *S-T* segment elevation of leads V_2, V_3 and V_6 and ventricular ectopic beats

with the unipolar (V) leads recorded around the chest in this case. In Figure I (Case 11) the main delay seems to be recorded in the *R* wave of lead V_9 at the left scapular line. However, it is noticeable that the *T* wave is upright over the left ventricular leads—a feature of many cases of "atypical bundle branch block" (Friedberg, 1950). The standard and unipolar limb leads in this case (Figure II) show the high voltage and *QRS* delay, and also display prominent but narrow *Q* waves in leads I and aVL. In this case a further electrocardiogram (Figure III) taken after six days of quinine therapy, consisting of 10 grains thrice daily, which relieved most of the myotonia, showed no change in the pattern of conduction delay, although the *S-T* segment in leads V_2, V_3 and V_4 had developed a "roller coaster" pattern. Similarly, neither potassium

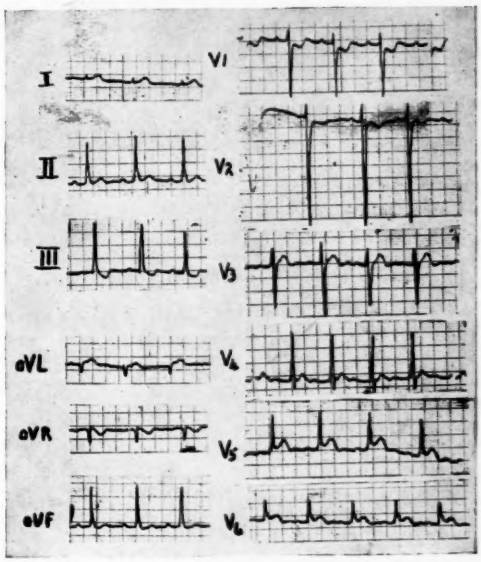

FIGURE VI

Case 13. Electrocardiogram taken on August 14, 1952, terminal bronchopneumonia. Note *S-T* segment elevation of leads V_5 and V_6, inversion of *T* wave in leads V_1 and V_2 with *S-T* segment depression in lead V_1

salts given by mouth (six grammes of mixed citrate and chloride) nor "Prostigmine" (2·5 milligrammes) given by injection were found to affect the *QRS* time.

Elevation of the *S-T* segment was also a feature of many of the tracings, being seen in six cases. This elevation in no case resembled that of myocardial infarction, having an upward concavity and never being associated with abnormal *Q* waves.

In Figures IV, V and VI one characteristic case is illustrated—that of Mr. P.S., aged fifty years (Case 13). The tracing shown in Figure VI was taken during the final few weeks of the

patient's illness, when he was suffering from gross bronchopneumonia with severe breathlessness and cyanosis. Comparison of Figures VI with Figures IV and V, which were recorded three months earlier, shows several points of great interest. In both tracings the *S-T* segment is elevated in lead V_6. In Figure VI elevation of the *S-T* segment in lead V_5 is also pronounced, as is elevation in lead aVL. In Figures IV and V elevation is also present in lead V_2, in lead aVF and in leads II and III.

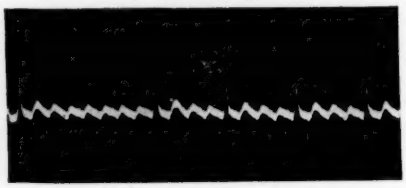

FIGURE VII

Case 1. Lead II, showing auricular flutter with varying 8 : 1 and 4 : 1 auriculo-ventricular block. This pattern easily reverted to normal with quinidine therapy

The *T* wave of leads V_1 and V_2 is upright or diphasic in Figure IV (the earlier tracing), but is distinctly inverted in the second tracing (Figure VI), when it seemed possible that the bronchopneumonia had produced a degree of right-sided heart strain, although no signs of frank congestive heart failure were present (Kilpatrick, 1951). The fact that elevation of the *S-T* segment over the left ventricle was present in both tracings suggests that this finding was not a reflexion of *S-T* depression over the right ventricle due to right ventricular strain. Besides this, similar elevation of the *S-T* segment has been noted in five other cases in which there was no question of pulmonary infection. Quinine, quinidine or potassium medication has not been found to affect the degree of elevation of the *S-T* segment. While *S-T* segment elevation of this type occurs infrequently in tracings of normal subjects, the frequency of its occurrence in this series is quite striking. However, the significance of the change is difficult to assess. In Figures IV and V frequent ventricular ectopic beats are shown. In some of these the *R* wave interrupts the preceding *T* wave, a feature noted by Smirk (1949) in various types of heart disease and shown to be of serious prognostic significance.

Also illustrated is an example of auricular flutter (Figure VII, Case 1) showing the varying 8 : 1 and 4 : 1 auriculo-ventricular block, and in Figure VIII (Case 5) is shown an example of atypical left bundle branch block.

Autopsy findings are available in two cases (Cases 2 and 6) only ; in neither was any gross or microscopic abnormality seen in the heart except in Case 6, in which the surface of the heart was recorded as having a fibrous appearance. In one further recent case not included in this series the electrocardiogram was normal, and at autopsy the heart was microscopically and macroscopically normal.

It seems likely that the cardiac changes can be grouped into two sections—those related to delayed conduction, and those more likely to be due to muscular changes such as the *S-T* segment elevation in the electrocardiogram and the tendency to congestive heart failure noted in one case in this series. Whereas changes in the autonomic nervous system might possibly account for the delay in conduction, the facts that " Prostigmine " did not affect the conduction time and that conduction delay seems to persist when there is sinus tachycardia suggest that such nervous influences do not account for the whole picture.

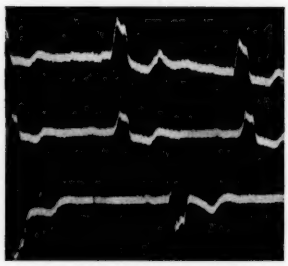

FIGURE VIII

Case 5. Leads I, II and III, showing left bundle branch block with the rather atypical *T* wave changes. An almost identical pattern was seen in two other cases of this series

The lack of any changes in the hearts examined *post mortem*, both in this series and in those of other authors, is surprising and suggests that the abnormality in the heart in this disease may be of a metabolic nature. The problem might be further clarified if more cases of *dystrophia myotonica* were examined in detail from the cardiac point of view, and if a post-mortem examination was performed in all possible cases, special reference being made to the heart both macroscopically and histologically.

CONCLUSIONS AND SUMMARY

In 18 cases of *dystrophia myotonica*, studies of the cardio-vascular system showed numerous abnormalities.

In two cases clinical abnormalities were present; in one heart failure was present, the reason for which was unaccountable. In the other aortic regurgitation developed before death, but *post mortem* the heart was not found to be grossly abnormal.

In 14 cases the electrocardiogram showed abnormalities. In six, concave *S-T* segment elevation was present. In four there was an atypical left bundle branch block or arborization block. Prolongation of the *P-R* interval was present in five. Other changes noted less frequently were auricular flutter, ventricular ectopic beats showing the "*R* on *T*" phenomenon, sino-auricular block, prolonged *Q·T* time and low *T* waves.

No evidence as to the cause of these abnormalities could be found; but it seems likely that there are changes in the cardiac muscle, possibly of a metabolic nature.

ACKNOWLEDGEMENTS

The writers have to thank colleagues who have permitted them to investigate their cases and to publish the results of some of the investigations. They also have to thank the Pathology Departments of the Auckland Hospital and of the University of Otago for permission to quote their post-mortem findings. They are indebted to the electrocardiography technicians of the Auckland Hospital and the Dunedin Hospital, and to the Photographic Unit, Dunedin Hospital and University of Otago Medical School.

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NON-KERATIN URIC ACID DETERMINATIONS IN GOUT.[1]

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It has been shown that urates are among the non-keratins (water-soluble organic substances residing in keratinous structures) of mammalian integument (Bolliger and Gross, 1952*a*, 1952*b*, 1954). In a few human patients the urate content of the keratinous appendages was found to be increased in gout and in long-standing severe renal insufficiency. This was observed mainly on toe nails (Bolliger and Gross, 1953*a*, 1953*b*). In the present investigation, the diagnostic significance of uric acid determinations in cases of gout was studied principally on head hair, but also on toe and finger nails and on pubic hair.

Methods

Hair and nails were rinsed with ether to remove contaminating material and dried at room temperature. Nails were scraped clean with a scalpel if further cleaning was required. A weighed sample of hair or nails was then extracted repeatedly with boiling water in a flask fitted with a reflux condenser or in a conical vessel covered by a funnel. Approximately 25 millilitres of water per gramme of hair were added for the first boiling out. After at least forty minutes' boiling, as much as possible of the extracting water was decanted. A fresh and approximately equal volume of water was added to the hair, which was again boiled out for about thirty minutes. This was followed by a third extraction of about ten minutes' duration with a smaller volume of water.[3]

The combined filtered extracts were concentrated to about 10 to 20 millilitres for each gramme of keratinous material extracted. The uric acid content was determined by Folin's "direct" method (1933), five millilitres of the concentrate being used, or less in cases of elevated uric acid content. This method supplies the "direct" uric acid value, which consists of true uric acid content and chromogen of unknown nature.

To obtain the "true" uric acid content, another five millilitres of the extract were incubated at 45° C. for two hours with 250 milligrammes of a preparation of the enzyme uricase and five millilitres of borate buffer (pH 9·2). After this the proteins of the uricase preparation were removed with two millilitres of 10% sodium tungstate solution and three millilitres of two-thirds normal sulphuric acid, and then Folin's "direct" method was applied to five millilitres of the incubated filtered sample. The difference in colour value before and after treatment with uricase was considered to be a measure of the true uric acid content of the extract. This method is referred to as the uricase method, and results obtained by it are called "uricase" values.

The ordinary grooming habits have comparatively little influence on the sparingly soluble uric acid present in hair. In toe nails the possible effect of leaching out of uric acid by grooming may be expected to be even smaller.

Materials

For control subjects head hair and nails were collected from 12 normal volunteers and from 20 patients of the Royal Prince Alfred Hospital, Sydney, not suffering from disorders of uric acid metabolism. Material from 16 patients, living or deceased, suffering from severe renal insufficiency was investigated.

Hair and nails of sufferers from gout were supplied by physicians who had these patients under their care. The diagnosis rested on the occurrence of repeated attacks of classical arthritis together with at least one of the following: presence of tophi, response to colchicine or raised blood uric acid level.

Results

Results in the control subjects are shown in Table I. In the normal subjects the uricase method gave values approximately two milligrammes per 100 grammes less than the direct

[1] Received on February 5, 1955.
[2] Working under a grant from the National Health and Medical Research Council.
[3] Extraction in the Soxhlet apparatus for four hours was subsequently found to be more convenient.

TABLE I

Uric Acid Content of Hair and Nails of Normals and Hospital Patients Living and Deceased, Excluding Those with Disturbed Uric Acid Metabolism

Subjects	Age (Years)	Method	Uric Acid Content of Hair (Milligrammes per 100 Grammes)		Uric Acid Content of Nails (Milligrammes per 100 Grammes)	
			Mean	Range	Mean	Range
Normal controls—12 ..	24 to 50	"Direct" ..	7	4 to 9	6	5 to 8
		"Uricase" ..	5	3 to 7	5	4 to 6
Patient controls—20 ..	21 to 79	"Direct" ..	8	4 to 12	8	6 to 11
		"Uricase" ..	6[1]	3 to 9	6[2]	3 to 8

[1] Test performed on 12 patients.
[2] Test performed on 14 patients.

method. The uric acid content of nails was not significantly different from that of hair by either method.

The values for patient controls were slightly higher than for the normal subjects, but the difference was not as great by the uricase method. Some of these results of uric acid determinations have been listed in detail in previous papers (Bolliger and Gross, 1953, 1954).

The results in 16 cases of renal insufficiency and elevated blood urea levels are shown in Table II. From 11 of these patients specimens were collected after death.

Five sufferers from chronic nephritis who were not yet in the terminal stage had normal hair and nail uric acid values (Cases 1 to 5). Of five deceased patients who exhibited severe but short-lived urea retention, nearly all had normal values in their toe nails (Cases 6 to 10). These normal values were exceeded by patients who died with severe urea retention lasting for more than one month (Cases 11 to 16). The head hair of these deceased patients contained greater amounts of uric acid than the nails. The reason for this is not clear.

Gout

Diagnostic details and results of uric acid estimations in 17 cases of gout are shown in Table III.

Direct estimations on head hair were carried out in 16 cases, and in 13 of these the uric acid values were definitely elevated. The uricase method was applied to the head hair of 11 of these patients; in 10 of these the uric acid content was elevated. Pubic hair from two patients with gout yielded essentially the same results as head hair.

TABLE II

Uric Acid Content of Head Hair and Toe Nails in Renal Insufficiency

Subject Number	Age (Yrs.)	Sex	Uric Acid Content of Hair (Milligrammes per 100 Grammes)		Uric Acid Content of Nails (Milligrammes per 100 Grammes)		Blood Urea Content (Milligrammes per 100 Millilitres)	Known Duration of Urea Retention (Months)	Diagnosis
			"Direct" Method	"Uricase" Method	"Direct" Method	"Uricase" Method			
1	22	F.	6	4	—	—	58	18	Chronic nephritis.
2	35	M.	8	—	—	—	109	6	Chronic nephritis
3	42	F.	7	—	5	—	89	3	Chronic nephritis
4	28	F.	7	—	6	—	153	2	Chronic nephritis
5	51	F.	8	6	6	—	174	12	Chronic nephritis
6	64	F.	—	—	8	6	125	<1	(*P.m.*[1]) Hypertension and nephrosclerosis
7	69	F.	—	—	9	6	307	<1	(*P.m.*) Pyelonephritis
8	65	M.	—	—	11	9	128	<1	(*P.m.*) Hypertension and nephrosclerosis
9	74	M.	—	—	8	6	272	<1	(*P.m.*) Pyelonephritis
10	84	M.	17	14	7	5	378	<1	(*P.m.*) Urinary retention
11	45	M.	26	24	15	12	445	6	(*P.m.*) Chronic nephritis
12	51	M.	—	—	18	14	428	2	(*P.m.*) Chronic nephritis
13	44	F.	—	—	19	14	442	2	(*P.m.*) Chronic nephritis
14	52	M.	—	—	13	11	231	3	(*P.m.*) Chronic nephritis
15	44	F.	20	17	16	14	257	>1	(*P.m.*) Hypertension and nephrosclerosis
16	34	F.	14	—	12	10	622	2	(*P.m.*) Pyelonephritis

[1] *Post mortem.*

TABLE III

Uric Acid Content of Head Hair and Toe Nails in Clinical Cases of Gout

Subject Number	Age (Yrs.)	Sex	Duration of Illness (Years)	Tophi	Colchicine Response	Blood Uric Acid[1] Content (Milligrammes per 100 Millilitres)	Uric Acid in Hair (Milligrammes per 100 Grammes)		Uric Acid in Nails (Milligrammes per 100 Grammes)		Comments
							"Direct"	"Uricase"	"Direct"	"Uricase"	
1	34	M.	13	+	+	6·4	34	28	29	26	Post-mortem specimen
							32	26	—	—	Post-mortem specimen, pubic hair
2	40	M.	12	0	+	11[2]	31	27	—	—	
3	42	M.	5	0	+	6	28	23	—	—	
							26	23	—	—	Test repeated after one month
4	64	M.	?	+	+	6·1; 4·6	24	—	19	14	
5	54	F.	—	—	+	6·0	22	—	14	—	
6	58	M.	2	0	+	5·8	21	19	—	—	
7	42	M.	23	+	+	4·2	20	17	14	—	
8	41	M.	18	+	+	—	20	—	—	—	
							18	—	—	—	Test repeated afte two months
9	48	M.	4	+	+	2	19	—	21	—	
10	41	M.	7	0	+	8·4	19	15	23	18	
							18	14	—	—	Pubic hair
11	45	M.	6	+	+	4·9	17	—	11	8	
12	36	M.	4	0	+	—	13	10	16	—	
13	61	M.	—	—	+	—	13	11	14	11	
14	53	M.	1	0	+	3·2; 4·2	—	—	15	—	
15	54	M.	1	+	0	4·4; 2·6	12	11	13	11	
16	30	M.	3	+	—	—	11	10	10	—	
17	39	M.	4	+	0	2·2	8	5	—	—	

[1] Blood uric acid determinations were performed in hospital laboratories
[2] Serum uric acid content.

The nail uric acid content was found by the direct method to be elevated in 10 out of 12 cases investigated (13 to 29 milligrammes per 100 grammes), and by the uricase method in five of six cases (11 to 26 milligrammes per 100 grammes).

The amount of non-uric acid chromogen was approximately the same in the hair and nails of both gout-free and gouty subjects, so that the more rapid and convenient "direct" method appeared to be satisfactory for most diagnostic purposes.

The blood uric acid values shown were estimated within a few weeks of the estimations on hair and nails. These determinations were performed at the hospitals to which these patients were attached or in private clinical laboratories.

DISCUSSION

While classical gout is readily diagnosed on clinical grounds, atypical cases are common and diagnosis may be difficult. A high blood or serum level of uric acid may help to establish the diagnosis, but there are a number of difficulties in the interpretation of blood or serum uric acid figures. Thus, even in established cases of gout with tophi, the blood uric acid level is variable and may be within normal limits at the time of investigation. It is unlikely that the uric acid content of nails or hair will vary except over long periods, and such estimations would appear, from our results, to provide a valuable confirmatory test when blood values are normal.

Theoretically the maximum solubility of uric acid in blood serum is about eight milligrammes per 100 millilitres, and consequently serum uric acid values higher than this cannot be expected even in the most advanced cases of gout (Hoffman, 1954). The amount of uric acid deposited in solid form in keratinous appendages is not limited to the same extent by solubility factors, which operate in blood serum, and values four times as high as those encountered in normal subjects have repeatedly been found by the specific "uricase" method in cases of gout with and without tophi.

The elevated urate content of keratinous structures in chronic renal insufficiency may lead to confusion in the case of suspected gout with associated renal disease. The present observations and those reported previously (Bolliger and Gross, 1953*b*) suggest that renal insufficiency leads to increase in keratinous urate only after prolonged and severe nitrogen retention; but in such cases the confirmation of the diagnosis of gout must depend on the assessment of all available evidence.

It may be pointed out that some clinicians emphasize the peculiarities of the nails of gout sufferers. For example, Thannhauser in his treatise on metabolism and its diseases (1929) states that changes in the nails are characteristic of gout, brittleness and splintering being a frequent symptom, and that every attack of gout leaves a trace in the form of an indentation at the nail fold; when the slow movement of the nail is borne in mind, it is thus possible to determine the time of an acute attack of gout. The present work suggests that indentations seen at the nail fold some time after an attack may arise from an increased deposition of uric acid, or from a suddenly diminished supply of it during the period of decreased blood uric acid level at the time of an acute attack.

SUMMARY

The uric acid content of hair and nails of normal subjects and of patients suffering from a variety of diseases including renal insufficiency and gout was determined by the "direct" method of Folin and by the "uricase" method.

Normal values obtained by the "direct" method were four to nine milligrammes per 100 grammes for hair and five to eight milligrammes per 100 grammes for nail parings. With the "uricase" method the maximal values were seven and six milligrammes per 100 grammes respectively. In patient controls, those with disturbed uric acid metabolism being excluded, maximal values were two to three milligrammes per 100 grammes higher.

In 16 cases of serious renal impairment the values were elevated only in the terminal stage of chronic renal disease, but not in long-lasting, mild disease. Severe but brief attacks of renal insufficiency did not materially increase the nail uric acid content.

Values were determined in 17 cases of gout. Results above normal either in hair or in nails were found in all but one of these. The highest values for the hair and nails of persons with gout were 28 and 26 milligrammes per 100 grammes respectively ("uricase" method). This suggests that uric acid determinations on hair or nails may be of diagnostic value in doubtful cases of gout in which blood values are normal.

Certain advantages of the method over the determination of blood levels are indicated.

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SOME OBSERVATIONS ON THE TREATMENT OF TUBERCULOUS PLEURAL EFFUSIONS.[1]

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IT is generally accepted that the treatment of tuberculous pleural effusion should be directed towards the eradication or control of tuberculosis in the body as a whole. Experience in a small unit for the treatment of tuberculous pleurisy with effusion has shown that there are complications of the effusion itself which have an adverse, and possibly lasting, effect upon the patient, and which of themselves merit attention quite apart from the general question of the treatment of tuberculosis.

An analysis has been made of the nature and frequency of the complications of pleural effusion, and of the effect of treatment upon them.

In particular an attempt has been made to determine the relationship, if any, which exists between both the size of the effusion and the age of the patient on the one hand, and any one of the following complications on the other: chronicity, recurrence, the development of pleural thickening and overt tuberculosis.

The value of certain forms of treatment has been assessed by their effect upon the incidence of these complications.

An attempt was made to determine whether aspiration should commence early in the course of the illness, or whether it should be carried out only if there is dyspnœa or if the fluid persists for an unduly long time, as has been advocated by many experienced physicians (Nicholson, 1953; Young, 1952). Although a number of physicians have advised early aspiration, we were unaware of any published account comparing the results obtained by the two forms of management. Lately Mackay-Dick and Rothnie (1954) found, in patients treated with antibacterial drugs and early aspiration, that the effusions persisted for a shorter time than in those treated by bed rest alone.

As we have been unable to find any report of a controlled study of the value of chemotherapy in the treatment of pleural effusion, this aspect has been examined also.

CLINICAL MATERIAL AND METHOD

We have studied 93 consecutive patients with pleural effusion admitted to a pleural effusion unit between 1951 and 1953. Two patients presented with bilateral effusions.

The patients were all males with a serous pleural effusion known, or presumed on clinical grounds, to be tuberculous. About two-thirds of the patients were aged under twenty-five years, while less than a fifth were aged over thirty-five years. The pleural effusion was the main manifestation of disease in all cases, but coexisting enlargement of the hilar glands, minor tuberculous disease of the lungs, or intrathoracic calcifications existed in 35 cases. The hilar enlargement was more common among the younger patients, while pulmonary disease was seen more commonly in the older groups.

In addition to this series of English cases, a group of 11 patients treated in an Australian repatriation hospital has been followed for four to ten years in an attempt to study the eventual outcome of residual pleural thickening. These latter patients had been treated for pleural effusion and had definite pleural thickening upon their discharge from hospital. The degree of pleural thickening in the follow-up radiographs has been compared with that present originally.

The brief case histories chosen as examples are from the Australian source mentioned above.

Classification of Cases

The following definitions have been used in classifying the cases. To avoid duplication, the two patients who presented with bilateral effusions have been classified according to the features associated with the larger of the two effusions. The maximum size of each effusion was estimated radiologically as follows: (i) small

[1] Received on June 6, 1955. This work was carried out mainly during the tenure of a Wunderly Travelling Scholarship of The Royal Australasian College of Physicians by one of us (A.H.C.). It formed the substance of a contribution to the Scientific Session of the meeting of The Royal Australasian College of Physicians in May, 1954, at Melbourne.

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effusions: those causing collapse of less than 20% of the volume of the lung; (ii) medium effusions: those causing collapse of more than 20% but less than 50% of the volume of the lung; (iii) large effusions: those causing collapse of more than 50% of the lung.

The duration of an effusion was assessed with some difficulty, as it was not easy to distinguish between a persistent effusion and thickened pleura. The results of attempted aspiration were taken as a guide; but when late aspiration was not carried out, a radiographic pleural shadow still decreasing fairly rapidly in size was taken as evidence of the presence of fluid.

A radiological pleural opacity was interpreted as pleural thickening when aspiration failed, or when the shadow remained little altered for several months.

The degree of pleural thickening was measured on a postero-anterior radiograph taken with the patient in the erect posture at the end of six months' treatment, or on his discharge from hospital. It was assessed as follows: (i) When the peripheral opaque area measured at least six by two centimetres in some part, the pleural thickening was classified as marked. (ii) Moderate pleural thickening was held to be present when the peripheral opaque area measured at least two by one centimetre in some part. (iii) Degrees of pleural thickening less than this were considered to be slight.

The spread of an effusion to the opposite side, and the recurrence of an effusion completely or partially absorbed, were both classified as recurrent effusion.

Treatment

All patients were treated by bed rest followed by gradual exercise unless complications developed. The average period of hospital treatment was six to eight months.

When chemotherapy was administered, it was in short courses, either soon after the onset of the effusion or after complications had occurred. When treatment with streptomycin, sodium PAS or isoniazid, alone or in combination, had been commenced within eight weeks of diagnosis and continued for at least one month, the patient was classified as having received chemotherapy. If chemotherapy had been administered for a shorter period or at a later date, then the case was classified in the "no chemotherapy" group.

An exception to this classification was made when the effect of chemotherapy upon recurrent effusion was considered. If chemotherapy commenced within eight weeks of diagnosis, but after the recurrence, then the case was classified in the "no chemotherapy" group.

Therapeutic aspiration was held to have been performed when aspiration was continued until almost all the fluid had been removed, and had ceased to form. When this procedure was commenced within the first month, the therapeutic aspiration was classified as early.

Patients not treated by early aspiration form the control group. In a number of these cases the fluid was partially aspirated early, but except for diagnostic purposes, in the majority aspiration was not performed until after the first month.

Comparison of Treatment Groups and Controls

All patients had commenced treatment elsewhere before admission to our unit. The treatment varied according to the views of the physician consulted initially. The treatment groups and their controls have been compared in Tables I and II. None of the differences between the groups is statistically significant. The treatment groups and controls are quite similar when compared for progression of the effusion and its size. There was a tendency for chemotherapy to be administered to older patients and to those in whom the condition had a severe onset. Of those patients in whom aspiration was performed early, a greater proportion had an acute onset and were aged

TABLE I

Background Data: Early Aspiration. Showing the Number of Cases and Percentage in Each Group

Group	Age (Years)			Onset		Dynamic Status Progression	Size of Effusion			Chemotherapy
	Under 20	20 to 34	35 and Over	Severe	Insidious		Small	Medium	Large	
Early aspiration, 19 patients	3 16%	13 68%	3 16%	12 63%	7 37%	5 26%	2 10%	12 63%	5 27%	10 52·6%
Controls, 74 patients	32 44%	30 40%	12 16%	31 42%	43 58%	22 29%	8 11%	52 70%	14 19%	22 29·7%

TABLE II

Background Data : Chemotherapy. Showing the Number of Cases and Percentage in Each Group

Group	Age (Years)			Onset		Dynamic Status Progression	Size of Effusion			Early Aspiration
	Under 20	20 to 34	35 and Over	Severe	Insidious		Small	Medium	Large	
Chemotherapy, 32 patients	11 34%	12 38%	9 28%	18 56%	14 44%	11 34%	4 13%	20 62%	8 25%	10 31%
No chemotherapy, 61 patients	24 40%	31 50%	6 10%	25 40%	36 60%	16 26%	6 10%	44 72%	11 18%	9 15%

between twenty and thirty-four years than the controls. However, there was no difference in the percentage aged over thirty-five years.

The severity of the onset was not found to have any relationship to the various complications of the effusions, so that the slight differences in this regard are unlikely to be important. The differences in age are distributed irregularly between the groups, and are not always in the right direction or of sufficient degree to have influenced the results more than slightly.

TABLE III

Effect of Size of Original Effusion on Persistence of Fluid[1]

Size of Effusion	Number of Patients	Number with Persistence of Fluid for Four Months or Longer
Small and medium ..	74	13
Large	19	9

[1] The large effusions were much more likely to persist for four months or longer than were small and medium effusions. $\chi^2=5\cdot84$; $n=1$; $P=<0\cdot02$.

There has been some overlap between the two treatments owing to a tendency to combine, and it might be thought that this would invalidate the results. This would be the case if both factors appeared to have an effect ; but when one form of treatment shows no effect and the other does, then it can be concluded that the result with the treatment showing no effect is not due to the overlap of treatments. Similarly, the favourable results obtained with other treatment can then be accepted as valid.

RESULTS

In the management of tuberculous pleural effusions, the following four important and frequent complications were encountered : (i) undue delay in reabsorption of the effusion ; (ii) pleural thickening ; (iii) recurrence of pleural effusion on the same or opposite side ; (iv) the development of pulmonary or extra-pulmonary tuberculosis.

Various other less frequent complications have not been analysed owing to their infrequency.

Delayed Absorption of Effusion

Slow absorption of the effusion was relatively common ; 24% of the patients still had an effusion after four months. In some, it was present for twelve months.

The time taken for the fluid to absorb was found to be related to the amount of fluid originally present (Table III). No relationship was found between the failure of an effusion to absorb and the age of the patient (Table IV).

TABLE IV

Effect of Age upon Delayed Absorption[1]

Age (Years)	Number of Patients	Number with Effusions not Absorbed in Four Months
Under 20	35	9
20 to 34	43	8
35 and over	15	5

[1] No relationship was found between the age of the patient and the chronicity of the effusion.

Thickened Pleura

Twelve patients (12·9%) were found to have marked pleural thickening, and 19 (20%) moderate pleural thickening at the end of the treatment. Pleural thickening most commonly follows large effusions (Table V), and is more frequent in the older patients (Table VI).

To obtain information about the permanence of thickened pleura, 11 patients with moderate or marked pleural thickening due to pleural effusion were followed for four to ten years. The pleural thickening diminished in all cases ; but when this was initially gross, considerable thickening usually remained, and pleural calcification was likely to develop.

Of five patients with marked pleural thickening, this remained marked in two, and became moderate in three by the end of the period of observation. In two cases pleural calcification had appeared. Similarly, of six patients with initial moderate pleural thickening this was still moderate in three and slight in three at the end of the observation period.

TABLE V

Effect of Size of Original Effusion on Residual Pleural Thickening[1]

Size of Effusion	Number of Patients	Number with Moderate or Marked Pleural Thickening
Small and medium ..	74	19
Large	19	12

[1] There was a greater frequency of moderate or marked pleural thickening following large effusions than after small and medium effusions. $\chi^2=7\cdot54$; $n=1$; $P=<0\cdot01$.

The following two cases are examples of permanent pleural thickening.

CASE I.—This patient was admitted to hospital with a large pleural effusion in January, 1944. When he was discharged seven months later he had marked pleural thickening. An X-ray film taken more than ten years after the onset still shows marked pleural thickening in which calcification is appearing. Movement of the left side of the chest is very restricted.

TABLE VI

Relationship of Age of Patient to Degree of Pleural Thickening[1]

Group	Number of Patients	Number with Moderate or Marked Pleural Thickening
Number aged under 35 years	78	21
Number aged over 35 years	15	10

[1] Older patients show a greater frequency of pleural thickening than younger ones. $\chi^2=7\cdot22$; $P=<0\cdot01$; $n=1$.

CASE II.—This patient was known to have had a large pleural effusion in 1921. An X-ray film taken more than thirty-two years later shows marked pleural calcification. He has had poor chest movement since 1921.

Recurrent Effusion

Recurrent effusion took place either as a recrudescence of the effusion on the same side or as a spread to the opposite side. In the series of 93 patients, a recrudescence occurred in eight, and in three other patients the effusion became bilateral.

TABLE VIII

The Relationship Between the Size of the Effusion and the Development of Pulmonary Tuberculosis[1]

Group	Number of Patients	Size of the Effusion		
		Large	Medium	Small
Overt pulmonary tuberculosis ..	8	1	6	1
No pulmonary tuberculosis ..	85	18	58	9

[1] The size of the effusion was not found to be related to the development of pulmonary tuberculosis.

Recurrent effusion was not influenced by the age of the patient, and was slightly more frequent after larger effusions; but this was not statistically significant (see Table VII).

TABLE IX

Relationship Between Age and the Development of Tuberculosis[1]

Age in Years	Number of Patients	Number Developing Overt Tuberculosis
Under 30	70	9
Over 30	23	0

[1] There is a trend which favours the younger patients developing pulmonary tuberculosis, although this is not statistically significant. This may be due to the small numbers.

Pulmonary and Extrapulmonary Tuberculosis

During the period of hospital observation, active pulmonary tuberculosis developed in eight cases and spinal tuberculosis in one. The development of overt tuberculosis was not found to be related to the size of the effusion (Table VIII). Overt tuberculosis occurred predominantly in the younger patients—all who developed this complication were aged under thirty years (Table IX). As observed by

TABLE VII.

The Effect of Age of the Patient and Size of Effusion on Recurrence of Effusion, showing the Number of Patients in Each Group.[1]

Group	Number of Patients	Patient's Age in Years			Size of Effusion		
		Under 20	20 to 34	35 and Over	Large	Medium	Small
Recurrent effusion ..	11	5	4	2	4	7	0
Without recurrence ..	82	30	39	13	15	57	10

[1] No statistically significant relationship was demonstrated between recurrent effusion and the age of the patient or the size of the effusion

Eberle (1949), the tuberculous complications were more frequent in patients with bilateral effusions. Of the five patients with bilateral effusions (two on presentation and three subsequently), three developed pulmonary tuberculosis, whereas of 88 patients with unilateral effusions only five developed pulmonary tuberculosis.

TABLE X

Early Aspiration and the Length of Time for which Effusion was Present.[1]

Aspiration	Number of Patients	Time for which Effusion was Present (Mean in Months)	Standard Deviation
Early therapeutic aspiration	19	2·63	1·28
Delayed or incomplete aspiration	74	3·89	2·49

[1] In patients treated by early therapeutic aspiration, the length of time for which the effusion lasted was shorter than in those treated by delayed or incomplete aspiration. $t=2·1$; $n=93$; $p=<0·05$.

THE EFFECT OF TREATMENT

Aspiration

In the present investigation, adequate and repeated aspiration commenced or attempted in the first month has been classified as early therapeutic aspiration. The results obtained by this procedure compare very favourably with those obtained by more conservative methods.

TABLE XI

Effect of Early Aspiration of Large Effusions on Degree of Residual Pleural Thickening[1]

Aspiration	Number of Patients	Number Developing Moderate or Marked Thickening
Early	5	0
Not early	14	12

[1] In the case of large effusions, early therapeutic aspiration reduced the incidence of moderate and marked pleural thickening. $\chi^2=8·18$; $P=<0·01$; $n=1$.

It was found that early complete aspiration had a significant effect in reducing the length of time for which an effusion persisted (Table X). Early aspiration greatly decreased residual pleural thickening, especially in the case of large effusions (Table XI). This effect was not so pronounced in the case of moderate and small effusions.

It was found that early aspiration made it possible to keep the lung well expanded until the fluid ceased to accumulate. When delayed, aspiration became difficult because of thickened pleura and fibrin deposits. The lung became encased in a layer of fibrous tissue, its re-expansion became slow, and the fluid re-accumulated rapidly after aspiration.

TABLE XII

The Effect upon Effusion of All Sizes of Therapeutic Aspiration Commencing in Different Months[1]

Therapeutic Aspiration	Number of Patients	Number Developing Marked or Moderate Pleural Thickening
Commencing in first month	19	3
Commencing in second month	9	4
Commencing after two months	9	9

[1] In the cases in which aspiration was carried out later than the first month, resolution was slow. Pleural thickening was not prevented when slow resolution was used as the criterion for aspiration.

Table XII shows the inferior results obtained when therapeutic aspiration was considered necessary, and attempted later than the first month.

The three groups compared were dissimilar, being selected on the basis of the need for aspiration after differing time intervals. The results show that when failure to resolve is the criterion used to select cases requiring aspiration, then pleural thickening can be anticipated.

TABLE XIII

Effect of Early Aspiration upon Recurrent Effusion and Development of Pulmonary Tuberculosis[1]

Aspiration	Number of Patients	Number Developing Recurrent Effusion	Number Developing Pulmonary Tuberculosis
Early	19	1	1
Not early ..	74	10	7

[1] No relationship was found between early aspiration and recurrent effusion or pulmonary tuberculosis.

Neither recurrent effusion nor overt pulmonary tuberculosis was found to be related to early aspiration (Table XIII).

Decortication

When a large effusion was still present after four to six months, expansion of the lung usually took many months, and was then incomplete owing to marked pleural thickening.

For this reason decortication of the lung was considered in such cases. However, in the series of 93, only one patient was submitted to decortication, but it is considered that this procedure has a place in the treatment of the large neglected effusion.

Chemotherapy

Chemotherapy appeared to be of value in preventing relapse of the pleurisy on the same or opposite side. Patients receiving chemotherapy for more than one month were less likely to develop a recurrence than those who received chemotherapy either not at all, or for a period up to one month (Table XIV). The patients were not followed for a sufficient time to allow a full assessment of the effect of chemotherapy upon the incidence of clinical tuberculosis; but when administered for three months or less, chemotherapy did not prevent the early development of pulmonary or extrapulmonary tuberculosis. Of the 33 patients who received chemotherapy, three developed pulmonary tuberculosis, and similarly of 60 patients who did not receive chemotherapy, five developed pulmonary tuberculosis.

TABLE XIV

Effect of Chemotherapy on Recurrent Effusion[1]

Chemotherapy	Number of Patients	Number Developing Recurrent Effusion
Chemotherapy given ..	31	0
No chemotherapy given	62	11

[1] There was a reduced incidence of recurrent effusion on the same or opposite side when chemotherapy was employed. $\chi^2 = 4 \cdot 64$; $n = 1$; $P = < 0 \cdot 05$.

TABLE XV

Effect of Chemotherapy upon Persistent Effusion and Pleural Thickening[1]

Chemotherapy	Number of	Number with Fluid Present More than Four Months	Number Developing Moderate or Marked Pleural Thickening
Chemotherapy given ..	33	7	11
No chemotherapy given	60	15	20

[1] Chemotherapy of short duration was not found to have any influence upon chronicity of the effusion or pleural thickening. This was in spite of the fact that a greater proportion of the chemotherapy group than of the controls were treated by early aspiration.

Chemotherapy without aspiration did not prevent chronicity of the effusion or thickened pleura (Table XV).

DISCUSSION

Chronicity of an effusion and marked pleural thickening have certain undesirable features. A persistent effusion impairs pulmonary function, frequently leads to pleural thickening, and may eventually rupture either internally or externally. Considerable impairment of pulmonary function may accompany thickening of the pleura. Pinner *et alii* (1942) found by bronchospirometry that pleural diseases, including the aftermath of pleurisy with effusion, were potent causes of impairment of pulmonary function. Our own clinical and fluoroscopic findings suggested that impairment of ventilation was directly proportionate to the amount of pleural thickening present.

Our results indicate the value of early therapeutic aspiration in avoiding persistent effusion and pleural thickening. Repeated aspiration was sometimes necessary owing to reaccumulation of the effusion. This reaccumulation may be related to the dynamic state of the effusion and not to the aspiration. In fact, the effusion continued to enlarge in one-third of the patients prior to aspiration. Presumably if aspiration had been performed during this progressive phase, the fluid would have inevitably reaccumulated. It may well be advantageous to allow an evolving effusion to reach its peak by delaying for two or three weeks before commencing complete aspiration. Therapeutic aspiration commencing within the first month did not lead to any serious complications.

The failure of chemotherapy to prevent either pleural thickening or the early development of pulmonary tuberculosis was disappointing, but may have been due to its relatively short period of administration. It was found that chemotherapy appeared to reduce the frequency of relapse of the effusion, and for this reason alone it appears of value. Also, D'Esopo and Medlar (1952) have suggested that prolonged courses of chemotherapy should be given in cases of pleurisy with effusion in order to minimize the subsequent development of pulmonary lesions. Thompson (1946) found that within five years of the onset of original symptoms, 25% of patients who had had pleurisy with effusion had developed clinical evidence of pulmonary disease, and that 80% of these did so within the first two years.

SUMMARY

In the series of 93 consecutive cases of pleural effusion, chronicity of effusion, pleural thickening and recurrence of the effusion were relatively frequent complications. Gross pleural

thickening may diminish in subsequent years, but seldom disappears.

Persistent fluid and pleural thickening can be largely avoided by adequate aspiration commencing within the first month.

Recurrence of effusion is less likely if chemotherapy is employed.

Whether chemotherapy will prevent the development of tuberculous complications was not determined, but short courses failed in this regard. The use of prolonged chemotherapy requires further exploration.

ACKNOWLEDGEMENTS

We should like to acknowledge our gratitude to Dr. John J. McCann for considerable help in the preparation of this article. Clinical observations of patients treated in repatriation hospitals have been used with the permission of the Chairman of the Repatriation Commission.

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CHRISTMAS DISEASE[1]

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IN 1952 Biggs *et alii* in Great Britain described a syndrome due to a blood-clotting deficiency which clinically resembled hæmophilia; however, the deficiency could be corrected by hæmophiliac blood. Independently Aggeler *et alii* (1952) and Schulman and Smith (1952) in the United States of America described similar cases, and even earlier Pavlovsky (1947) and Koller *et alii* (1950) had described cases which now fit into this category.

Mersky (1950) showed that normal blood added to hæmophiliac blood would shorten its prolonged coagulation time, whereas the addition of other hæmophiliac blood would not do so. Biggs *et alii* showed that the blood of their patients, who previously had been regarded as hæmophiliacs, had a corrective effect similar to that of normal blood.

As the first patient with this disease was named Christmas, Biggs *et alii* termed the disease Christmas disease, and suggested that its cause was a deficiency of the Christmas factor. American investigators have introduced the term plasma thromboplastin component (P.T.C.) in lieu of Christmas factor; Fantl and Sawers (1954*a*) in this country have suggested that the deficiency should be known as β-prothromboplastin deficiency to contrast with the α-prothromboplastin deficiency of hæmophilia.

Biggs *et alii* have investigated the physical properties of the missing component, and have stressed its stability on storage, its great concentration in normal and hæmophiliac serum and its ready adsorption to aluminium hydroxide; in these and other properties it is most distinct from anti-hæmophiliac globulin.

In the present investigation 21 "hæmophiliac" patients have been studied, and of these five have been found to be suffering from Christmas disease.

METHODS AND MATERIALS

All blood was carefully collected by a clean venepuncture into paraffin-lined syringes. Plasma was obtained by mixing the blood with one-tenth volume of 1·34% sodium citrate solution and centrifuging the mixture at 3000 revolutions per minute for ten minutes. Coagulation times were measured by the Lee and White method at 37° C. in tubes of internal diameter of nine millimetres. Prothrombin times (plasma) were determined by Quick's one-stage method and the serum prothrombin times (prothrombin consumption test) by a modified Quick's method; the normal for the latter was regarded as over forty-five seconds at the end of one hour.

Recalcified clotting times were estimated at 37° C. by the use of 0·02 molar calcium chloride solution. "Alumina" plasma was made by the addition of aluminium hydroxide suspension to the plasma in the proportion 1:9. The thromboplastin generation test was carried out by the method of Biggs and Douglas (1953). In principle the patient's serum, deficient in Christmas factor but with normal factor VII content, is added to a system containing all other components necessary for thromboplastin generation—namely, alumina plasma (containing anti-hæmophiliac globulin and factor V), platelet suspension and calcium. At one minute intervals samples (0·1 millilitre) are transferred to prothrombin-fibrinogen mixture and the clotting time is observed. This will depend on the amount of thromboplastin generated at the time of transfer. Thromboplastin is maximal at approximately four minutes when, if the serum under test is normal, the clotting time of the indicator mixture is approximately fifteen seconds. With each test a normal control is set up and the results are expressed as the following index (see Table III):

$$\frac{\text{Clotting time for control}}{\text{Clotting time for test mixture}} \times 100.$$

[1] Received on June 27, 1955.

[2] Adolf Basser Fellow in Clinical Research.

CASE REPORTS

CASES I AND II.—These patients were brothers. The elder boy, aged thirteen years, had been considered at the age of two years to be suffering from hæmophilia ; at that time hæmorrhage lasting for several days followed trauma to his ear, but ceased promptly after a blood transfusion. Numerous hæmorrhagic episodes had occurred, including epistaxis, hæmaturia, muscle and joint hæmorrhages and hæmorrhage following tooth extraction, and some had required blood transfusion.

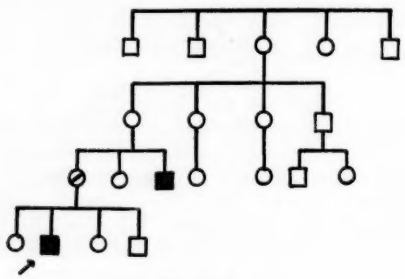

FIGURE I
Family tree (Case II)

In the younger brother, now aged ten and a half years, the condition manifested itself at the age of eleven months, when seven days' hæmorrhage followed trauma to the lips ; the bleeding stopped only after a blood transfusion. He bruised easily, but had less severe bleeding than his brother.

There was no family history of hæmorrhagic disease for four generations, with the exception of the boys' mother, who had a tendency to bruise easily and had bled severely after tooth extraction.

CASE III.—A boy, aged eight years, was circumcised as an infant without trouble, but had hæmorrhage into a buttock at the age of eleven months, and at eighteen months required a blood transfusion for the control of a sublingual hæmatoma. Several transfusions had been required since that time, but a flexion deformity of the right knee had been successfully manipulated after the administration of fresh plasma.

His mother's brother had died at the age of four years, after a "lung hæmorrhage". He had bled profusely at circumcision and had had other hæmorrhagic episodes. The mother had no tendency to bleed.

CASE IV.—A man, aged twenty-four years, gave a history of prolonged bleeding from cuts and especially after tooth extraction. He bruised easily, but never experienced severe joint hæmorrhages. Two brothers were affected ; but his mother was an adopted child, and no further history is available.

CASE V.—A man, aged forty-four years, had suffered hæmorrhagic episodes throughout his life. He had required many admissions to hospital and many transfusions for intestinal bleeding, which mainly presented as melæna. He was a very heavy alcoholic, and bowel bleeding often followed his alcoholic excesses ; he had X-ray evidence of scarring of the duodenal cap. Deep X-ray irradiation of his stomach produced achlorhydria, after which he had melæna once in eleven months ; in the two years prior to irradiation he had required admission to hospital ten times for melæna. He had never experienced a hæmarthrosis. Two of his brothers were bleeders, but one had died from a "ruptured stomach" with bleeding and the other from myocardial disease. The grandfather was a known bleeder, who died from a bleeding peptic ulcer.

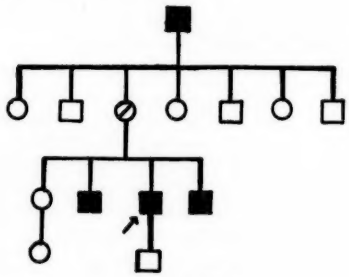

FIGURE II
Family tree (Case V)

EXPERIMENTAL RESULTS

The coagulation times were greatly prolonged in three of the five cases, and of the remaining two patients, one (Case IV) was not a severe bleeder. Prothrombin consumption times were abnormal in all cases, but in Case IV the results

TABLE I
Laboratory Findings in Five Cases of Christmas Disease

Case Number	Coagulation Time	Prothrombin Index (Percentage)[1]	Serum Prothrombin Times (Seconds)[1]		Bleeding Time (Minutes)	Platelet Count per Cubic Millimetre
			One Hour	Two Hours		
I	63 minutes	100	13·5	16	3	330,000
II	60 minutes	100	14	20	2	320,000
III	12 minutes	100	15	20	2·5	187,000
IV	11 minutes	100	24	27	2·5	165,000
V	>12 hours	90	—	23	2	248,000

[1] Thromboplastin preparation employed gave a normal prothrombin time (one-stage) of 13·5 seconds.

were the least abnormal. The platelet counts, bleeding times and prothrombin times (one-stage) were normal (Table I). Mixing of plasmas and recalcification showed that hæmophiliac plasma corrected the defect in coagulation (Table II).

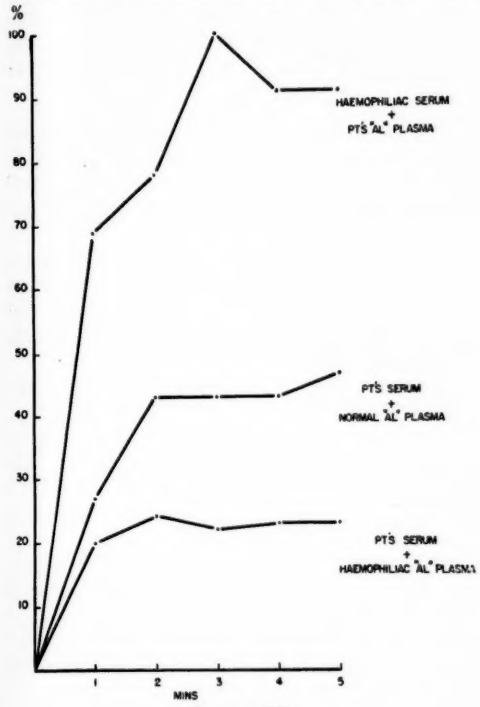

FIGURE III

Graphic representation of thromboplastin generation with the use of blood from Case I

Thromboplastin generation tests were carried out on all patients to demonstrate the absence of the serum factor and the presence of anti-hæmophiliac globulin, and the results are set out in table form (Table III). A typical series of results from tests in which blood from Case I was used are shown in Figure III.

TABLE II

Mutual Correction of Recalcified Clotting Times (Seconds) by Christmas Disease and Hæmophiliac Plasma Mixtures

Case Number	Added Hæmophiliac Plasma					
	100%	80%	60%	40%	20%	0%
I	345	350	145	120	250	270
II	—	—	—	—	—	—
III	370	—	120	120	—	165
IV	380	—	150	150	—	230
V	>600	200	190	190	305	406

DISCUSSION

Christmas disease has been established as an entity distinct from hæmophilia, and at least 27 cases have been described which fit this diagnosis. Seven cases were reported by Biggs *et alii* (1952) in their original article, and others have been reported as follows: Koller (1950)

TABLE III

Thromboplastin Generation Expressed in Terms of Percentage of Thromboplastin Generated

Case Number	Minutes											
	1	2	3	4	5	6	1	2	3	4	5	6
	Normal Serum *plus* Patient's "Alumina" Plasma						Hæmophiliac Serum *plus* Patient's "Alumina" Plasma					
I	65	55	79	69	79	79	69	78	100	91	91	—
II	68	89	94	100	100	—	62	86	100	100	—	—
III	59	86	90	95	100	100	—	—	—	—	—	—
IV	27	83	75	100	88	—	74	82	87	83	93	100
V	59	86	90	95	100	100	74	87	87	100	93	—
	Patient's Serum *plus* Normal "Alumina" Plasma						Patient's Serum *plus* Hæmophiliac "Alumina" Plasma					
I	27	43	43	43	47	—	20	24	22	23	23	—
II	22	28	33	40	33	—	23	33	40	36	—	—
III	19	38	53	53	61	61	—	—	—	—	—	—
IV	9	11	—	21	27	29	—	—	—	—	—	—
V	19	38	54	54	61	65	16	31	70	57	54	55

one case; Van Creveld and Paulssen (1953), one case; Aggeler *et alii* (1952), one case; Poole (1953), one case; Schulman and Smith (1952), one case; White *et alii* (1953), one case; Lewis and Ferguson (1953), three cases; Brinkhaus *et alii* (1954), one case; Rosenthal and Sanders (1954), five cases; Fantl and Sawers (1954) in this country, six cases.

Clinically the presence of bowel hæmorrhages dermal ecchymoses and hæmarthroses, and prolonged bleeding following tooth extraction, suggest the diagnosis of hæmophilia, especially if there is a family history of "bleeders". The two adult patients in this group do not show the same degree of degenerative arthritis as is usually found in hæmophiliacs of the same age group. Van Creveld and Paulssen (1953) remarked upon the lack of joint involvement in their case.

The family histories in Cases III and V support the concept of Biggs *et alii* (1952) and of Rosenthal and Sanders (1954) that the disease is transmitted to males by a female carrier as a recessive sex-linked dominant. However, both the abovementioned groups agree that the carrier state of the female may not be asymptomatic, as some subjects show clinical evidence of a bleeding tendency and they may also have abnormal serum prothrombin times. This is supported by the bleeding of the mother of the first two patients (Cases I and II), who had an abnormal prothrombin consumption with a serum prothrombin time of twenty-two seconds at the end of two hours after coagulation of her blood.

Deficiency of the Christmas factor causes thromboplastin generation to be slow and the quantity of thromboplastin formed to be small, as shown in the thromboplastin generation test. The role of the Christmas factor in the generation of thromboplastin has been investigated by Biggs, Douglas and McFarlane (1953), who have suggested that the Christmas factor acts as a catalyst or as an enzyme; they have shown that it is activated by contact and reacts with factor V, which is consumed. Further clarification has resulted from the studies of Fantl and Sawers (1954*b*), who have concluded from their observations that α-prothromboplastin (anti-hæmophiliac globulin) is the precursor of plasma thromboplastin, and that β-prothromboplastin (Christmas factor) is a co-factor essential for its rapid production.

The differentiation of hæmophilia and Christmas disease is of considerable clinical importance, and depends on laboratory study. The hæmophiliac patient requires large volumes of fresh blood to obtain a sufficient concentration of anti-hæmophiliac globulin to allow coagulation to occur, whereas the patient with Christmas disease will obtain good coagulation with smaller volumes of blood, which does not need to be fresh, because of the stability of the Christmas factor (Rosenthal and Sanders, 1954).

SUMMARY

The clinical details of five patients suffering from Christmas disease are described. These patients were previously diagnosed as hæmophiliacs, and formed part of a group of 21 bleeders who were investigated.

The diagnosis depended on laboratory tests showing, in the patients' blood, diminished prothrombin consumption, defective thromboplastin generation and correction of the clotting defect by addition of hæmophiliac plasma.

Clinically and genetically the patients were indistinguishable from true hæmophiliacs, although the severity of the bleeding appeared to be less. The five patients were from four families, in all of which other members were affected.

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SOME LONG-TERM EFFECTS OF ANÆSTHESIA, MERCURIAL DIURESIS, OR ALTERATION OF BLOOD VOLUME ON THE CONTROL OF BODY WATER CONTENT[1]

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DURING the past few years increasing attention has been paid to the long-term overall features of water metabolism, particularly those concerned in the control of body water volume (Lowe, 1951, 1952, 1953; Lowe and Sayers, 1952).

A study of the normal range and pattern of day-to-day variations in water balance (Fowler, 1955*a*) led to the recognition of an unexpected slow phase in the equilibration of body water content (Fowler, 1955*b*). It was found, both in non-œdematous patients and in healthy rabbits, that after some moderate disturbance of water balance there is often a series of excessive fluctuations of body water content which subside only after several days to the range of fluctuations characteristic of normal.

This overall pattern was analogous to an earlier observation (Lowe, 1951) that in œdematous patients returning to normal there are large cyclical fluctuations of their body water content which may take many days to subside. It is thought that this sort of balance pattern indicates a disturbance of the normal volume-controlling mechanisms.

In the present series of experiments it was found that similar disturbances of the overall pattern of water balance often followed brief anæsthesia, a single injection of a mercurial diuretic, or an alteration of blood volume.

The results of these diverse interferences are considered in the light of the hypothesis, already advanced (Lowe, 1953), that two or more separate mechanisms are concerned in the control of body water content, and that at least one of these mechanisms is affected by the volume either of total body water or of one of its compartments.

[1] Received on June 1, 1955.

[2] Victor Y. and Margaret Kimpton Research Scholar, 1954.

PROCEDURES

This account of procedures is an outline only. Further details, and the accuracy of the methods used, have already been discussed in previous papers (Fowler, 1955*a*, 1955*b*).

Daily measurements were made of the water intake, urinary output and body weight of healthy adult rabbits observed under defined standard conditions.

Crude fluid balance and weight-derived fluid balance curves were drawn from these measurements.

The crude fluid balance is simply the measurable water intake *minus* the urinary output. It is plotted on the same scale as the weight-derived curve, but with an arbitrary origin, since no correction is made for insensible water gains and losses.

The weight-derived balance is a curve of daily weight changes. In these experiments, as in the earlier studies, there was a close qualitative resemblance between the crude and the weight-derived balance curves, and therefore the daily weight changes can be taken as predominantly changes in body water content.

As the weights are far more accurate than the crude fluid balance measurements, the weight-derived balance curves are preferred as the best available estimate of water balance. Accordingly, the observations presented here are based mainly on these weight-derived curves.

Experimental interferences were made only after the rabbits had been observed to be in a steady state of water balance for a control period of at least five days. Horizontal lines drawn on the weight-derived balance charts indicate the maximum range of fluctuations of body water content during each of these control periods.

With the exception of Rabbit I, all the rabbits were allowed water *ad libitum*. Instead

of water, Rabbit I received 300 to 400 grammes of fresh green cabbage daily. This allowed it a liberal although limited choice of intake at a level well above its minimum daily requirement, which would have been about 50 to 100 millilitres of water.

OBSERVATIONS

The observations are presented graphically in Figures I to VI, which show the long-term effects on water balance of the following interferences.

Anæsthesia

"Nembutal" was given intravenously to two rabbits in the following amounts relative to body weight: 33 milligrammes per kilogram to Rabbit 1 (Figure IA); 23 milligrammes per kilogram to Rabbit 8 (Figure IB). Initially both rabbits were for about fifteen minutes in a plane of light surgical anæsthesia, then each recovered gradually during the next four to five hours.

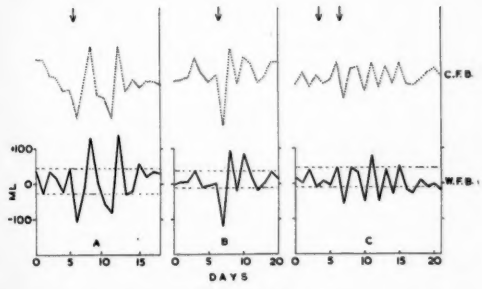

FIGURE I

In this and all the succeeding figures, "C.F.B." stands for crude fluid balance and "W.F.B." for weight-derived fluid balance, and each arrow indicates an interference described in the text

Rabbit 26 (Figure IC) was lightly anæsthetized with ether for half an hour, but there was no obvious effect on its water balance during the next three days. It was then anæsthetized again with ether, and this time it was kept in a deep surgical plane for fifteen minutes, then in a light plane for a further period of one hour.

Although the three illustrated patterns of disturbance are individually different, they present a common overall picture of excessive fluctuations of body water content, subsiding only after several days to the control range of fluctuations.

Injection of a Mercurial Diuretic

A single intramuscular injection of a mercurial diuretic was given to each of three rabbits in the following doses relative to body weight: "Neptal", 3·2 milligrammes per kilogram to Rabbit 1 (Figure IIA); mersalyl, 3·4 milligrammes per kilogram to Rabbit 27 (Figure IIB); mersalyl, 9·3 milligrammes per kilogram to Rabbit 29 (Figure IIC). For rabbits with grossly restricted water intakes the minimum toxic dose of this type of mercurial compound

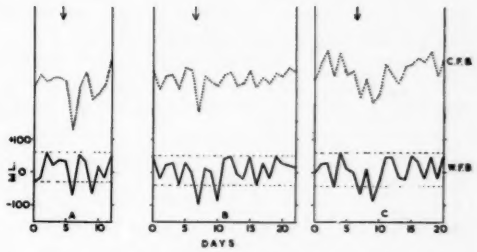

FIGURE II

is 11·5 milligrammes per kilogram, which causes death by rapid dehydration (Fourneau and Melville, 1931). Therefore the amounts given to these rabbits, which had liberal water intakes, would have been well below toxic limits. For the average adult patient two cubic centimetres of mersalyl represent a dose of about three milligrammes per kilogram, so that in at least two of the experiments the dosage was comparable with that which is commonly used clinically.

A series of excessive fluctuations of body water content can be seen to be a feature common to these three responses.

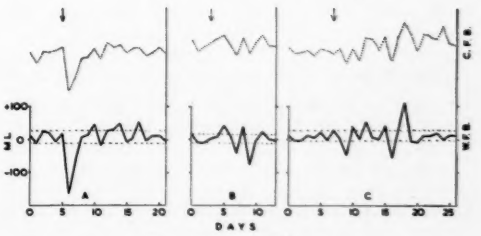

FIGURE III

Increase of Blood Volume

To expand blood volume, an intravenous injection of dextran,[1] of homologous whole blood, of serum, or of cells suspended in an equal volume of 0·9% sodium chloride solution was given at the rate of one millilitre per minute in the following amounts per kilogram of body weight: dextran, eight millilitres, to

[1] "Intradex", Crookes Laboratories.

Rabbit 30 (Figure IIIA); serum, seven millilitres, to Rabbit 27 (Figure IIIB); whole blood, 20 millilitres, to Rabbit 30 (Figure IIIC); whole blood, 10 millilitres, to Rabbit 29 (Figure IV); cells in saline, 20 millilitres, to Rabbit 29 (Figure IV); dextran, 11 millilitres, to Rabbit 26 (Figure V).

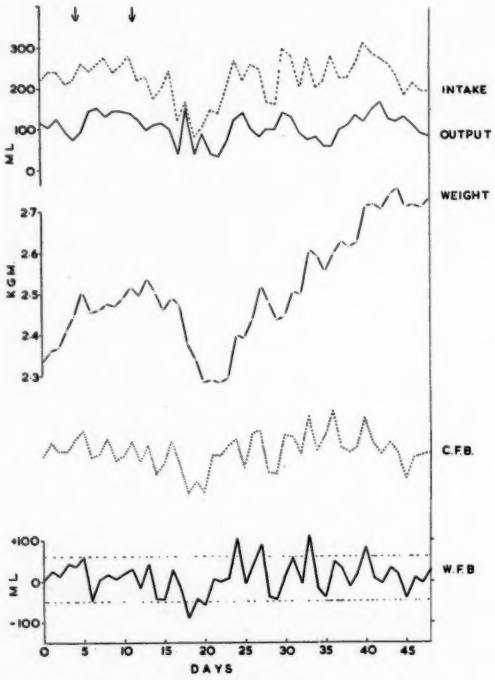

FIGURE IV

Since rabbits have a mean blood volume of 70 millilitres per kilogram (Courtice, 1943), these interferences represented initial increases in the vicinity of 10% to 30% of blood volume. These seemingly moderate increases of blood volume were followed by surprisingly prolonged upsets of water balance, particularly in Rabbits 29 and 26, whose intake, output and weight curves have been shown in addition to the balances in Figures IV and V respectively. It can be seen that concurrently with the excessive fluctuations of the water balances there were gross alterations in the levels and overall patterns of these other curves, starting in a definite progression from the time of interference and showing a slow return trend towards a steady state.

Considerable upsets of the overall patterns of intake, output and body weight were found in nearly all the other experiments. However, there seemed to be no consistent direction or pattern of change in these curves, and they have been omitted from the other charts so as not to confuse the overall resulting picture of disturbed volume control.

Nevertheless it does seem important to draw attention to these long-term effects on other aspects of water metabolism—as, for example, the greatly varying levels of water turnover of Rabbits 26 and 29.

It seems also, from the different plateaux in these two weight curves, that at an altered rate of turnover there may be day-to-day

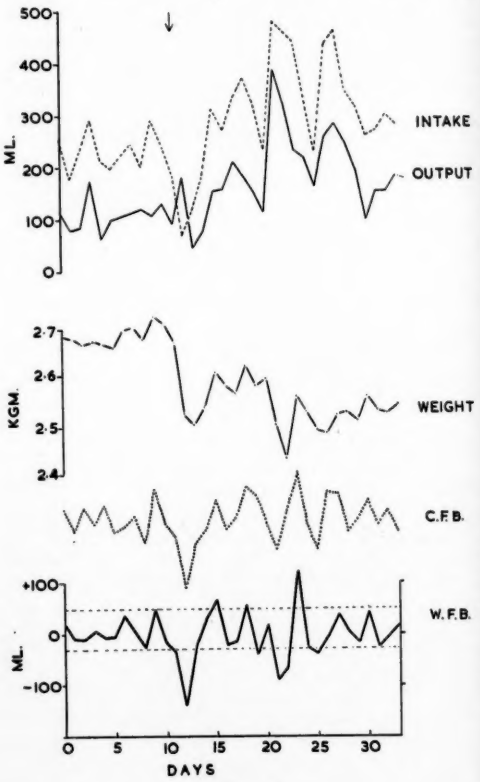

FIGURE V

fluctuations of normal range around a mean total volume set at a different level, either for a few days (Figure IV) or for quite lengthy periods (Figure V).

In Rabbit 29 the first interference with blood volume produced only a transient slight upset of water balance, and the rabbit quickly returned to a steady state for the five days

preceding the next interference. However, presumably many of the cells from the first transfusion could still have survived, so that the prolonged effect in this instance may have been due to summation of the two interferences.

Decrease of Blood Volume

Three rabbits were each bled as rapidly as possible from a marginal ear vein to obtain the following amounts relative to body weight: 11·6 millilitres per kilogram from Rabbit 30 (Figure VIA), 10·6 millilitres per kilogram from Rabbit 26 (Figure VIB), 13·5 millilitres per kilogram from Rabbit 27 (Figure VIC).

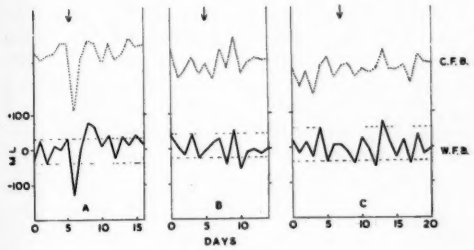

FIGURE VI

In Rabbits 30 and 26 there were definite disturbances of water balance for some days after the bleeding, although it is noticeable that these effects were not so pronounced as those following comparable increases of blood volume.

In Rabbit 27 slightly increased fluctuations of the weight-derived balance curve began some days after the hæmorrhage; but there was such a poor correlation between the crude and weight-derived balance curves that in this instance the evidence for any long-term effect on volume control is equivocal.

DISCUSSION

The kidney has for long been held to play a major part in the control of body water content. In fact, most of the investigations of this control have up till now dealt chiefly with the rate of urinary excretion of water and electrolytes, but usually for relatively short periods and with arbitrarily fixed conditions of water intake. Typical of these studies are the experiments cited later as evidence for the existence of a volume receptor.

However, such short-term observations can give only an incomplete account of the overall features of volume control, since normally a particular change of urine flow can soon be followed by other changes in intake and output which may compensate for, exaggerate or reverse the initial alteration of body water content. There is some need, therefore, for further investigation and description of the overall patterns of water balance resulting from this freedom of control.

It is well known, for instance, that mercurial diuretics can produce initially a negative water balance, so to some extent the present observations on mercurial effects merely confirm the role of the kidney in volume regulation. However, they do supplement the short-term information by showing how prolonged and fluctuant in character the resulting disturbance of volume control can be in a normal animal.

From acute experiments it is also known that a change of blood volume can cause a change of urine flow. Welt and Orloff (1951) have reviewed much of this work, and have noted the several conflicting findings. They concluded that an increase of blood volume usually led to diuresis, although they found that the time of day was one important factor influencing the response. However, even in twenty-four hour urine flows there may be no consistent direction or pattern of change following blood volume expansion, as can be seen from the two responses shown in Figures IV and V.

Nevertheless, following a variety of blood volume changes, the overall patterns of the balance curves shown in Figures III, IV, V and VI possess one feature in common. This is a series of excessive fluctuations of water balance, indicating that the control of body water content can be disturbed by volume changes in the vascular compartment. Since in these few experiments the effects on volume control seemed less pronounced after decreases than after increases of blood volume, it may be that the restoration of blood volume after moderate hæmorrhage takes less time than the removal from the vascular compartment of a comparable load of one of the substances which expand blood volume.

Next to be considered is whether a severe initial disturbance of renal function can explain the long-term effects observed after anæsthesia. This possibility seems unlikely, since the administration of ether to rabbits has only transient neurogenic effects on the kidney, which disappear during the anæsthesia (Smith, 1951), and even deep barbiturate anæsthesia produces no disturbance of renal function in rabbits (Forster, 1947). It would seem, therefore, that the central nervous system must in some way be concerned in the control of body water content; but the present anæsthetic experiments provide no further information

concerning the two most likely mechanisms, either one or both of which may have been disturbed. These two likely mechanisms are the osmoreceptors of the central nervous system already demonstrated by Verney (1946), and a receptor sensitive to a change in the volume of some fraction of body water which has been postulated for a number of years. There is some evidence for such a centre in the cranial cavity (Viar *et alii*, 1951; Lombardo *et alii*, 1951; Lusk, Viar and Harrison, 1952; Pearce, Newman and Birmingham, 1954), while other experiments suggest that there are volume receptors in the intrathoracic vascular bed (Gauer *et alii*, 1950).

In these earlier relatively short-term experiments the predominant finding after volume disturbances has been an altered rate of sodium excretion, whereas the results of blood volume interference reported here show rather more directly that the overall control of body water volume can be disturbed. These long-term effects are compatible with the idea of a volume receptor situated somewhere in the vascular tree, with either an intracranial or an intrathoracic locus. These two possibilities are not mutually exclusive, but can readily be fitted into the concepts of body volume regulation put forward by Lowe (1953).

The body has many of the features of an "open" physical system involving water (Lowe and Sayers, 1952), including the phenomenon of "overswing" during equilibration (Fowler, 1955*b*). Such a system has the property of self-regulation when disturbed (Burton, 1939; von Bertalanffy, 1950), and so it might be thought that the open system notion alone was enough to account for the regulation of body water volume. However, a simple physical model of an open system handling water and possessing only one, or even two, controlling mechanisms, cannot mimic all the patterns of intake, output and fluid balance found in ward patients, and so it is necessary to postulate a greater number of controlling forces which probably include cardiac action, osmotic pressure and the volume of some fraction of body water (Lowe, 1953).

This scheme of a system with multiple controls gains support from the results of the present series of experiments, which indicate that the central nervous system, the renal tubules and the volume of some part of the vascular tree are all involved in the control of body water content, because interference with any one of them is often, though not invariably, followed by prolonged disturbances of volume control.

But the periods of anæsthesia employed were only brief, and likewise the mercurial diuretics were probably excreted fairly rapidly, since they have a half-life in the body of only a few hours (Burch *et alii*, 1950). It is not suggested, therefore, that a prolonged pattern of excessive fluctuations of body water content means a continuing action of the interfering agent on the particular mechanism it affects, although this may very well be true in the case of the blood volume expanders.

What seems quite likely, particularly after anæsthesia or mercurial diuresis, is that once the control of body water content is sufficiently disturbed, the mechanisms concerned with equilibration may overcorrect a few times in each direction before a steady state is again reached. Slow equilibrations with "overswings" of this sort have already been observed after dehydration and overhydration, and are regarded as a normal response of the volume-controlling mechanisms (Fowler, 1955*b*).

As in these earlier experiments, it was again noted here that in spite of the general similarities already mentioned in the overall patterns of response, the individual patterns varied extremely in their detail. It is not known as yet how to predict whether a particular interference will be followed by a particular pattern of recovery or, in fact, by any response at all. A similar observation is that of Lowe (1952), who found that in patients the overall response to a mercurial diuretic can vary greatly, and seems to depend on whether the interference is made during a phase of water retention or a phase of water loss. On theoretical grounds it would be expected that, starting from identical initial external conditions, an open system might well respond in different fashions on separate occasions, provided that the internal conditions and energy output of the system had altered in the meantime. The foregoing observations, then, could well be consistent with the behaviour of an open system.

SUMMARY

An open system with multiple controlling forces could account for the regulation of body water content. This hypothesis has been elaborated in previous work from this research unit and has been based largely on observations from patients in abnormal states of fluid balance.

The results of the present experiments on healthy rabbits have complemented these clinical observations and give additional support to the hypothesis.

In these animals it was found that a series of excessive fluctuations of body water content, which gradually subsided to the range of fluctuations characteristic of normal, often followed a period of brief anæsthesia, mercurial diuresis or an alteration of blood volume. On the basis of previous work, this sort of overall balance pattern is taken to indicate some disturbance of the normal mechanisms controlling body water volume. It is concluded that the central nervous system, the renal tubules and the volume of some part of the vascular tree are at least three of the factors concerned in volume regulation, and that in these observations there is further evidence for the existence of a volume receptor.

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Proceedings of The Royal Australasian College of Physicians

ANNUAL MEETING, 1955

THE Annual Meeting of the College in 1955 was held in Sydney from May 10 to May 14. It was attended by Fellows and Members representative of all the Australian States and of New Zealand. The President, Dr. C. G. McDonald, was in the chair. The President of the Royal College of Physicians of London, Sir Russell Brain, Bt., was present at the meeting.

COLLEGE CEREMONY

The Annual Ceremony of the College was held in the Great Hall of the University of Sydney on the evening of Wednesday, May 11, 1955. An audience of 900 was present.

Address by the President

In his opening address the President spoke as follows:

"Your Excellency, Mr. Prime Minister, Mr. President of the Royal College of Physicians of London, Mr. Chancellor, Ladies and Gentlemen, I wish in the first instance to express our deep appreciation of the presence of His Excellency the Governor-General at this ceremony. He does great honour to this Royal College by coming here.

"We are honoured also by the presence of the Prime Minister and his wife, Dame Pattie Menzies. I extend to them a warm welcome from this College.

"Further, there arrived by air from England yesterday the President of the Royal College of Physicians of London, Sir Russell Brain, and his wife, Lady Brain, both of whom are with us this evening. By their visit to us they are forging a golden link between that ancient College founded in the reign of Henry VIII by the great Linacre, and our College, her so much younger sister.

"I should like also to say how glad we are to welcome the President of the Royal Australasian College of Surgeons, Professor Harold Dew; the representative of the Royal College of Obstetricians and Gynæcologists, Professor Bruce Mayes; and the representative of the College of Radiologists of Australasia, Dr. D. G. Maitland.

"It is also a great honour to have with us representatives of the Churches, including His Grace Archbishop Mowll, His Grace Archbishop Eris O'Brien and the Reverend R. B. Lew, all of whom we are happy to see here; representatives of the Armed Services; the President of the Federal Council of the British Medical Association in Australia, Sir Archibald Collins; members of the judiciary, leaders of our own profession and distinguished persons in every walk of life.

"It is customary for the College to hold each year a public ceremony in one of the cities of Australia or New Zealand. If we do it with some show of pomp and circumstance in which you, our audience, join, it is because, proud as we are of the task to which we are called, we look to you for much of that inspiration which will still linger with us when we become immersed in our work.

"We are a band of physicians devoted to the study and practice of internal medicine and our ranks are open to those medical graduates who by examination at the post-graduate level show themselves fitted to practise medicine, as distinct from surgery, obstetrics and the surgical specialties, at a high standard of efficiency. We are thus an examining body, largely patterned on the model of the Royal College of Physicians of London, and constituted to award higher qualifications to those graduates who wish to specialize in medicine and its auxiliary branches. We also aim to advance the study of medicine by means of scientific meetings and by the promotion of research.

"But we are more than this. Although we are but seventeen years old, we are joint recipients with others of a tradition of learning, high conduct and charity, handed down to us by physicians through the ages. In a world torn by strife, when the passions of cruelty and oppression are easily unleashed, it is the boast of medicine that so many of her sons have dedicated their lives to the relief of suffering. While medical knowledge may be, and has been, transformed within a generation, human values are permanent and all-important. It is the physician's privilege to practise the virtues of the past while he advances along the pathway of knowledge. He tries to effect that genuine synthesis of tradition and progress which is the aim of every great profession and indeed of every branch of learning.

"You already know much of our progress in the art and science of medicine, and most of you have at some time or other met us in the consulting-room, or by the bed-side. But tonight we seek rather to direct your attention to the tradition of medicine and to the part played by physicians in the social history of mankind."

Conferring of Honorary Fellowships

The Censor-in-Chief then presented to the President for admission as Honorary Fellows of the College His Excellency Field-Marshal Sir William Slim, G.C.B., G.C.M.G., G.C.V.O., G.B.E., D.S.O., M.C.; the Right Honourable Robert Gordon Menzies, C.H., Q.C., M.P.; and Sir Walter Russell Brain, Bt., M.D., F.R.C.P. (London).

Presentation of Field-Marshal Sir William Slim.—The Censor-in-Chief presented Field-Marshal Sir William Slim in the following terms:

"Mr. President, by unanimous resolution of Council, I have the duty, honour and privilege to present to you for admission to the Honorary Fellowship of the

College His Excellency the Governor-General, Field-Marshal Sir William Slim.

"We honour him not only because of the exalted office which he holds as Her Majesty's representative in Australia, but also for his personal qualities of character and high courage. Indeed it may be said that His Excellency's name is written large in the history of our time. No less an historian than Sir Winston Churchill has recently written in glowing terms of the forceful and brilliant leadership of the then General Slim of the magnificent 14th Army in the campaigns in Burma in 1944 and 1945.

"Australians and New Zealanders are said to have a high regard for a man who carves for himself a brilliant career unaided. His Excellency's progress in the British Army, from private soldier to Field-Marshal and Chief of the Imperial General Staff, is surely epic.

"Mr. President, I present to you His Excellency Field-Marshal Sir William Slim, Governor-General of the Commonwealth, for admission as a Fellow of the College *honoris causa*."

Presentation of the Right Honourable Robert Gordon Menzies. The Censor-in-Chief then presented the Prime Minister and spoke as follows:

"Mr. President, for the first time in the history of this College, I have the high honour to present to you for admission to the Honorary Fellowship of the College a native-born Australian who is not a graduate in medicine.

"Robert Gordon Menzies, Companion of Honour, Privy Councillor, Queen's Counsel, First Minister of Her Majesty in this Commonwealth, has been Prime Minister of Australia for a record term. But it is not only for this distinction that the College desires to do him honour. It has in mind his eminence as a leader, his distinction in his own profession, his fame as a scholar and his services to the nation. He is one of the great statesmen of our time.

"Mr. President, I present to you the Right Honourable Robert Gordon Menzies, Prime Minister of Australia, for admission as a Fellow of the College *honoris causa*."

Presentation of Sir Russell Brain. In presenting Sir Russell Brain the Censor-in-Chief made the following citation:

"Mr. President, I present to you for admission to the Honorary Fellowship of the College, Sir Walter Russell Brain, Baronet, Doctor of Medicine, President of the Royal College of Physicians of London.

"Sir Russell Brain is the distinguished holder of an office which stretches back four and a half centuries in the history of England, to when Henry VIII was on the throne and Thomas Linacre, his personal physician, founded the College of Physicians by Royal Charter.

"A brilliant clinical teacher, Sir Russell Brain has made many outstanding contributions to the science of medicine. He bears in the medical world an international reputation as a neurologist. By virtue not only of his office, but also of his great intellectual qualities, he is a foremost leader of British medicine.

"Mr. President, I present to you Sir Walter Russell Brain, President of the Royal College of Physicians, London, for admission as a Fellow of the College *honoris causa*."

Ceremonial of Admission. The ceremonial of admission of Honorary Fellows was followed by the presentation of newly admitted Fellows and Members.

Address by His Excellency the Governor-General

Field-Marshal Sir William Slim, addressing the audience, said:

"I thank you most sincerely, Mr. President, for the honour you have done me, an honour which for special reasons I particularly value. But I must confess that when I stand before any kind of a medical gathering I find myself overcome by a great deal of diffidence. I think that might be attributed to the memory I have of so many quite inspiring medical boards before which I have appeared and some of whose decisions I have managed to circumvent. Those amongst you who are psychiatrists might possibly trace this feeling of trepidation back further. It is just forty years ago since with some little discomfort I was raised up in a bed in a military hospital so that three medical officers could view me; and a colonel, who held in his hand one of those X-ray photographs which was not very good, addressed his two colleagues in words which have rather stuck in my mind: 'You will observe that the left lung is completely collapsed, that the heart is displaced into the cavity three inches, that the scapula is fractured and the head of the humerus is shattered.' This news made me rather sorry for myself, and I was hoping for a few words of encouragement, when the colonel suddenly turned to his two junior colleagues and said: 'This is really very good clinical material.' Somehow over the years every time I stand up before a medical gathering as I am doing now, I am always wondering in my mind what class of clinical material the colonel would put me in now. Very seriously, however, I regard the medical profession not only with respect but with immense gratitude. Not only for personal reasons, but on a much wider field of events in the war do I owe much to doctors.

"It was my lot to command an Army which was fighting the most vicious of enemies in what was called the worst theatre in the war, in the worst climate in the world for half the year, and in the worst breeding place for the most painful and destructive diseases—in Burma. We were losing for every man wounded or killed 120 evacuated sick. The evacuation rate was 13 per 1000, and we calculated that in three to four months the whole Army would have vanished. We were terribly short of doctors, tragically short of nurses and equipment, and we remained like that till the end of the war. Yet that grim picture of a rapidly wasting army in 1943 was turned in the beginning of 1945 into that of the healthiest army. The sick rate was one in 1000, and the transformation was due to the skill, courage and devotion of the medical services. I yield to no one in my admiration for surgeons. Surgical teams operated far forward, often right in the front line. Their successes were marvellous, and they played a more spectacular role. But the men who saved the army were the physicians. They healed the sick, but they did something more important than that: they prevented men from getting sick at all. My army not only could not have existed; they could not have won, without the physicians. They kept our men healthy. It was they who devised the protective measures that saved hundreds or thousands of men, and it was their advice which I was able to carry out which led to the reduction of the sick rate.

"Now, Mr. President, I think you will understand why I said I had particular reasons to be gratified by the honour which you have done me. The memory of the achievements and devotion of my physicians under the most difficult conditions and against the obstacles of man and nature makes me humble and

proud to be associated with them even in an honorary capacity.

"There is one point about the work they did. Their skill and devotion showed a very large capacity for discipline. Good doctors are not much good without good discipline. In the 14th Army we were fortunate that we had both. From the earliest recorded times physicians played a vital part in the life of their patients. That part is now rapidly increasing. It is not only increasing; it is perhaps changing. In the past the physician was a sort of companion and medical adviser, fatherly confessor and well-loved friend of the family. It has become much more difficult, and will become still more difficult, for him to play that invaluable role—more difficult, but not less desirable. It seems to me that medicine and physicians in particular are going through a testing time. They have to adjust themselves, not only to the advances of medical science, but also to the changes which are taking place in the conditions under which they work. I have no doubt that The Royal Australasian College of Physicians, true to its great traditions and to the honour of the noble profession it represents, will deeply consider and wisely counsel upon these matters—matters on which the true happiness and the real prosperity of Australia will depend. I wish the College well, and I thank you, Mr. President, for the very great honour which you have bestowed upon me."

Address by the President of the Royal College of Physicians of London

Sir Russell Brain spoke as follows:

"Mr. President, I find this a very moving occasion. I have received a great honour, for which I thank you all most warmly, and in which I know the London College will feel that it shares. But the Honorary Fellowship of this College is more than an honour; it is an expression of fellowship; it gives me a share in the traditions of your two great countires, and a second home which belongs to me and to which I am privileged to belong. I am proud of the honour and I am touched by the kindness with which you have conferred it, and both are far beyond my deserts.

"I was determined if it was possible to come and receive it in person. You, Sir, were kind enough to say it could be conferred *in absentia*, and I could have received it by post, but in comparison with coming that would have been like the difference between the 'x' at the end of a letter and the real thing. It was never so important as it is today that citizens of the Commonwealth should get to know the people of the sister countries in their own homes. We welcome many Australian and New Zealand doctors in Great Britain; you receive an increasing number of medical visitors from us with a generosity and hospitality of which they never cease to speak. But I believe we need, all the more therefore, to get together at what Sir Winston Churchill calls 'the summit', so that we can understand each other's problems and see how we can help each other.

"It was never easy to be a good doctor or to teach students to become good doctors. Today it is more difficult than ever, because we live in an age of ever-accumulating facts and ever-developing techniques. Both knowledge and technology are essential in medicine, but besides knowledge there is wisdom and besides technology there is art. We welcome the new facts and the new technical methods, wherever they come from, but let us make sure that we do not sacrifice the great traditions of British medicine to which we all owe what is best in our professional lives.

"What is the essence of that tradition? I believe it is twofold: first, it emphasizes clinical examination. Clinical examination is the foundation of new knowledge, because it alone can bring to a focus the light that comes from the scientific disciplines. It is also the basis of diagnosis, because it alone can filter the information derived from diagnostic methods and extract what is valuable.

"Then, with clinical examination goes the comprehensive outlook, which sees the patient as a whole. In these days of specialism it is necessary to emphasize this, but there is no reason why the specialist should not regard the patient as a whole. Ideally the general physician should look at the angles from the standpoint of the whole man, while the specialist regards the whole man from the standpoint of his particular angle.

"I have brought with me today a symbol of our common heritage, which I am going to ask you to accept as a gift from the Royal College of Physicians of London to The Royal Australasian College of Physicians. It is a replica of the gold-headed cane."

Presentation of the Gold-Headed Cane. In presenting the cane to the President, Sir Russell Brain read the following message from the Royal College of Physicians of London:

> We, the President and Fellows of the Royal College of Physicians of London, meeting in Comitia on April 28th, 1955, send by the hand of our President greetings to The Royal Australasian College of Physicians.
>
> With these greetings we have great pleasure in presenting to your College a copy of our Gold-Headed Cane. The cane originally belonged to Dr. John Radcliffe who carried it with him on his visits to patients, as the custom was in the Seventeenth and Eighteenth Centuries. In 1714 he presented it to Dr. Richard Mead whom he considered a worthy successor. It then passed to Dr. Anthony Askew, Dr. William Pitcairn, his nephew David, and Dr. Matthew Baillie. All were distinguished Fellows of this College and their Arms are engraved on the handle of the cane. The memoirs of this venerable companion of physicians as edited by Dr. William Macmichael, a Registrar of this College, accompanies this gift.
>
> Our two Colleges are united by a common tradition in Medicine and by the constant interchange of new Knowledge. We welcome this opportunity for strengthening the ties of friendship which already exist between us, and we offer to our sister College every good wish for her continued prosperity.

The President accepted the replica of the gold-headed cane and expressed the deep appreciation of the College for this gift.

Arthur E. Mills Memorial Oration

The Right Honourable R. G. Menzies, Prime Minister of Australia, then delivered the Arthur E. Mills Memorial Oration, "Medicine, Politics and the Law" (see *The Medical Journal of Australia*, 1955, July 30, page 149). In his opening remarks Mr. Menzies expressed his appreciation of the honour of Honorary Fellowship conferred upon him by the College, which he said would be a cherished memory.

Conclusion of the Ceremony

At the conclusion of the Ceremony guests were entertained at supper in the Union Refectory.

SCIENTIFIC SESSIONS

Two scientific sessions were held in the Stawell Hall of the College. The following contributions were given: "Cardio-vascular Research", by T. E. Lowe; "An Analysis of the Value of Medical Care in a Group of Repatriation Male Duodenal Ulcer Patients", by S. J. M. Goulston; "The Occurrence of Pancreatitis with Viral Hepatitis", by R. A. Joske; "The Mechanism of 'Squatting' in the Tetralogy of Fallot", by Douglas Stuckey; "Congenital Non-Spherocytic Hæmolytic Anæmia", by G. C. de Gruchy; "Complement in Pathogenesis and Diagnosis of Acquired Hæmolytic Anæmia", by Ralph Reader; "Progressive Bronchiectasis", by Howard Williams; "The Relation of Electrocardiographic Findings to Prognosis in Myocardial Infarction", by W. A. Seldon (by invitation).

A lecture was delivered by Sir Russell Brain on the subject "The Neurology of the Cervical Spine".

An abstract has been received of the paper "Congenital Non-Spherocytic Hæmolytic Anæmia", presented by G. C. de Gruchy, as follows:

> There are four well-recognized varieties of hæmolytic anæmia due to congenital abnormalities of the red cells—namely, hereditary spherocytosis (congenital acholuric jaundice), Mediterranean anæmia (Cooley's anæmia, thalassæmia), sickle-cell anæmia, and hereditary ovalocytosis. Recently several less well-recognized varieties which differ both clinically and pathologically from the above types have been described. This paper describes twelve such cases. Investigations have included studies of the family history, red cell morphology, osmotic and mechanical fragility tests, the auto-hæmolysis test with and without the addition of glucose, biochemical examinations including determination of the hæmoglobin type, red cell proto-porphyrin and serum iron, red cell survival and the effect of splenectomy. On the basis of these studies the cases fall roughly into the following groups:
>
> Group I, in which the cells appear morphologically normal, have fresh osmotic and mechanical fragilities, normal or increased auto-hæmolysis on incubation and contain a normal adult hæmoglobin. Of four such patients two have not responded to splenectomy, one has shown partial improvement and one has not been subjected to splenectomy.
>
> Group II, in which the red cells show considerable variation in size and shape, with normal osmotic and mechanical fragilities. This condition has been found in identical twins, one of whom underwent splenectomy and obtained a partial remission. This patient (aged seventeen years) also has gout, a rare association of congenital hæmolytic anæmia.
>
> Group III, in which the cells appear morphologically normal except for the presence of a moderate number of target cells, contain a small amount of fœtal hæmoglobin, and show increased resistance to saline solutions and a normal mechanical fragility. Three patients in one family with this condition have not been subjected to splenectomy.
>
> Group IV, in which the cells appear morphologically normal except for the presence of a moderate number of oval cells (not true elliptocytes), have a normal osmotic and a slightly raised mechanical fragility and contain normal adult hæmoglobin. Two patients, father and son, in this group have responded well to splenectomy.
>
> Group V, in which the red cells show considerable macrocytosis and anisocytosis, normal osmotic and mechanical fragility, a small amount of fœtal hæmoglobin and a slightly raised red cell proto-porphyrin. There is only one patient in this group, and the condition has not responded to splenectomy.
>
> In Australia, the major problem in diagnosis is to distinguish these patients, who have a clinical picture of acholuric jaundice, from patients with classical acholuric jaundice—that is, with hereditary spherocytosis. Careful examination of the morphology of the red cells, and quantitative osmotic fragility tests, both before and after incubation, should enable this distinction to be made. The problem is most difficult in relation to those patients with morphologically normal cells, for whom it is especially important, as in general these patients respond poorly to splenectomy.

CLINICAL MEETINGS

Clinical meetings were held in the Stawell Hall, and in the Robert Scot Skirving Lecture Theatre at the Royal Prince Alfred Hospital. The following demonstrations were given: "Phæochromocytoma", Justin Markell; "Tuberculous Meningitis with Recovery", H. Maynard Rennie; "*Epilepsy Partialis Continua*", W. J. Burke; "Chronic Progressive Polyneuritis with Tremor", George Selby; "Milkman's Syndrome", George Hall; "*Lupus Erythematosus* and *Porphyria Cutanea Tarda*", R. D. Puflett; "Hypoprothrombinæmia", James Isbister; "*Lupus Erythematosus* Phenomenon with Hæmolytic Anæmia", F. Hales Wilson; "Bronchiectasis with Cerebritis and Macrocytic Anæmia", Maurice Joseph.

COLLEGE DINNER

The College Dinner was held at the Royal Sydney Golf Club on the evening of Thursday, May 12, 1955. It was attended by 150 Fellows and Members, the guest of honour being the President of the Royal College of Physicians of London, Sir Russell Brain. The President proposed the toast of the Royal College of Physicians of London, and Dr. A. D. S. Whyte, the New Zealand Vice-President, spoke in support. In his response Sir Russell Brain spoke of the development of the Royal Colleges of Physicians and their influence on the standard of medicine in the community. He emphasized the importance both of developing a closer relationship between the Royal Colleges and of integrating their activities at the Commonwealth level.

OFFICE-BEARERS

Council. The annual election of Councillors resulted in the reelection of the following Councillors who are Fellows: Sir Charles Blackburn, Dr. Clive Fitts, Dr. T. M. Greenaway, Dr. Guy Lendon, Dr. J. A. D. Iverach (N.Z.) and Dr. E. G. Sayers (N.Z.). Dr. H. W. Garlick was elected to the vacancy created by the retirement of Dr. J. J. Billings, a Member Councillor.

Honorary Treasurer. Leave of absence was granted to the Honorary Treasurer, Dr. W. P. MacCallum, during his absence overseas from July to October inclusive. Dr. Bruce Hall was appointed acting Honorary Treasurer for this period.

Boards of Censors. Dr. Clive Fitts retired from the Australian Board of Censors. Dr. Eric Clarke and Dr. K. B. Noad were reappointed to the Board, and Dr. C. B. Sangster was appointed to fill the third vacancy. Dr. I. M. Allen retired from the New Zealand Board of Censors. Dr. C. R. Burns and Dr. S. L. Ludbrook were reappointed to the Board, and Dr. E. H. Roche was appointed to fill the third vacancy.

RESEARCH ADVISORY COMMITTEE

The following were appointed to the Research Advisory Committee for the period 1955-1957: Dr. S. A. Smith (Chairman), the President of the College or his nominee, the Honorary Treasurer of the College, the Honorary Secretary of the College, Professor H. R. Dew, Professor Lorimer Dods, Professor J. C. Eccles, Professor E. Ford, Dr. A. H. Tebbutt, Dr. Ian Wood. Consultant Panel: Sir Macfarlane Burnet, Professor A. H. Baldwin, Dr. Ruthven Blackburn, Dr. F. B. Byrom, Professor A. J. Canny, Dr. F. C. Courtice, Dr. E. H. Derrick, Dr. M. R. Lemberg, Dr. T. E. Lowe, Dr. Ian Mackerras.

MEMBERSHIP

Admission of Fellows. The following Fellows were admitted after election at the meeting of the General Body of Fellows on May 11, 1955: under Article 44, H. F. Bettinger; under Article 42, Alice M. Bush, D. G. Hamilton, Margaret M. Henderson, S. G. Nelson, B. A. Serjeant, R. J. Walsh and J. F. McCulloch (*in absentia*).

Admission of Members. The following candidates, who were successful at an examination held in New Zealand in February, 1955, were admitted *in absentia* to Membership on May 11, 1955: W. M. W. Brookfield, R. H. Culpan, P. W. Dykes, G. F. Hall, R. W. Hornabrook, J. D. McCreanor, J. R. Presland, D. H. H. Pullon, F. T. Shannon, C. M. Stubbs, J. M. Tweed, M. H. Watson, R. A. D. Wigley. The following candidates, who were successful at an examination held in Australia in April-May, 1955, were admitted in person to Membership: D. T. Church, B. D. Cotton, P. Ebeling, A. W. T. Edwards, K. F. Fairley, D. A. Ferguson, T. M. Ferrier, W. S. C. Hare, R. A. B. Holland, R. G. Lewis, K. H. McLean, D. C. Maddison, B. W. Neal, R. S. Packard, J. S. Penington, R. D. Spooner, H. C. Weekes. T. J. Constance, of New South Wales, was admitted to Membership under the special provisions of Article 37.

Honours. Honours have been bestowed by Her Majesty the Queen upon the following Fellows of the College: Sir Darcy Cowan, of South Australia, Knight Bachelor; Dr. J. L. Grove, of Tasmania, and F. G. Morgan, of Victoria, Commanders of the Order of the British Empire.

Obituary. The Council records with regret the death of Sir Archibald Collins, Rear Admiral D. A. Pritchard and Dr. W. C. Sawers, of New South Wales, who were Fellows, and of Dr. J. M. Wogan, of New Zealand, a Member of the College.

Membership Roll. The College roll at July 1, 1955, consisted of 313 Fellows and 448 Members.

GENERAL

Sir Arthur Sims Commonwealth Travelling Professors, 1956. The appointment has been announced of two Sir Arthur Sims Commonwealth Travelling Professors for 1956. They are Sir Lionel Whitby, of Cambridge, England, who will visit Australia and New Zealand, and Sir Geoffrey Keynes, of London, who will visit Canada and South Africa.

Assistant Honorary Librarian. Dr. M. F. Deck has been appointed as Assistant Honorary Librarian of the College.

Future Meetings of the College. In 1956 the annual meeting will be held in Wellington, New Zealand, from March 20 to 24, and the ordinary meeting will be held in Melbourne. In 1957 the annual meeting will be held in Brisbane.

Visit of Sir Russell Brain, P.R.C.P. The President of the Royal College of Physicians in London, Sir Russell Brain, visited Australia and New Zealand in May, 1955. He was accompanied by Lady Brain. The primary purpose of his visit was to attend the annual meeting of the College in Sydney. It was the first occasion upon which a President of the London College had visited the Australasian College, and it was felt that this was not only an occasion of historical importance to the College, but also of immense value in strengthening the ties that exist between physicians throughout the British Commonwealth. In addition Sir Russell and Lady Brain visited Canberra, Melbourne, Auckland, Wellington, Christchurch and Dunedin. In all these centres Sir Russell Brain gave lectures and visited various hospitals and institutes.

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